(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2002 (27.12.2002)

PCT

(10) International Publication Number
WO 02/102829 A2

(51) International Patent Classification[7]: C07K

(21) International Application Number: PCT/US02/19220

(22) International Filing Date: 17 June 2002 (17.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/298,098 15 June 2001 (15.06.2001) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/102829 A2

(54) Title: CROSS-REACTIVE MONOCLONAL AND POLYCLONAL ANTIBODIES WHICH RECOGNIZE SURFACE PROTEINS FROM COAGULASE-NEGATIVE STAPHYLOCOCCI AND STAPHYLOCOCCUS AUREUS

(57) Abstract: Polyclonal and monoclonal antibodies which are cross-reactive to both coagulase-positive staphylococcus bacteria, such as S. *hemolyticus*, are provided which can recognize surface proteins from both coagulase-positive and coagulase negative staph bacteria. The antibodies may be generated from surface proteins that have been isolated on the basis of characteristics that may be common between S. *aureus* and coagulase-negative staphylococci, and these recombinant surface proteins are used to generate the antibodies of the invention. There is also provided vaccines and methods which utilize these proteins and antibodies for the treatment or protection against a wide variety of staphylococcal infections.

CROSS-REACTIVE MONOCLONAL AND POLYCLONAL ANTIBODIES WHICH RECOGNIZE SURFACE PROTEINS FROM COAGULASE-NEGATIVE STAPHYLOCOCCI AND STAPHYLOCOCCUS AUREUS

Cross Reference to Related Applications

The present application claims the benefit of U.S. provisional application Ser. No. 60/298,098 filed June 15, 2001.

Field of the Invention

The present invention relates in general to surface proteins from *Staphylococcus aureus* and their active regions such as their A domains which have homologue proteins on coagulase-negative Staphylococci such as *S. epidermidis* and *S. hemolyticus* as well as antibodies which recognize said proteins, and in particular to isolated monoclonal and polyclonal antibodies which recognize specific proteins from *Staphylococcus aureus* and coagulase-negative Staphylococci and which are cross-reactive against *S. aureus* and coagulase-negative Staphylococci and can thus be utilized in vaccines and methods useful for preventing or treating a wide variety of infections caused by staphylococcal bacteria.

Background of the Invention

The successful colonization of the host is a process required for most microorganisms to cause infections in animals and humans. Microbial adhesion is the first crucial step in a series of events that can eventually lead to disease. Pathogenic microorganisms colonize the host by attaching to host tissues or serum conditioned implanted biomaterials, such as catheters, artificial joints, and vascular grafts, through specific adhesins present on the surface of the bacteria. MSCRAMM®s (Microbial Surface Components Recognizing Adhesive Matrix Molecules) are a family of cell surface adhesins that recognize and specifically bind to distinct components in the host's extracellular matrix. Once the bacteria have successfully adhered and colonized host tissues, their physiology is dramatically altered and damaging components such as toxins and proteolytic enzymes are secreted. Moreover, adherent bacteria often produce a biofilm and quickly become more resistant to the killing effect of most antibiotics.

S. aureus causes a spectrum of infections that range from cutaneous lesions such as wound infections, impetigo, and furuncles to life-threatening conditions that include pneumonia, septic arthritis, sepsis, endocarditis, and biomaterial related infections. *S. aureus* is known to express a repertoire of different MSCRAMMs that can act individually or in concert to facilitate microbial adhesion to specific host tissue components. In addition, another type of staphylococcus bacteria is identified as the coagulase-negative bacteria, including such species as *S. epidermidis* and *S. hemolyticus* which are also have been known to express MSCRAMMs, and which also are responsible for a wide range of bacterial infections and related diseases. In this regard, MSCRAMMs generally provide an excellent target for immunological attack by antibodies, both polyclonal and monoclonal antibodies.

However, because antibodies by nature are very specific and in the case of different types of Staphylococci, such as *S. aureus* on one hand (coagulase-positive) and *S. epidermidis* and *S. hemolyticus* on the other (coagulase-negative), it has still remained a significant problem to develop antibodies that exhibit cross-reactivity across the different types of bacteria. Such cross-reactive antibodies are particularly desirable because of their potential in immunizing human and animal patients and providing protection against infections caused by both types of Staphylococcal bacteria, namely coagulase-positive bacteria such as *S. aureus* and the coagulase-negative bacteria, such as *S. epidermidis* and *S. hemolyticus*. Such antibodies would thus be extremely useful in preventing or treating a wide variety of the infections caused by staphylococcal bacteria.

Summary of the Invention

Accordingly, it is an object of the present invention to provide monoclonal antibodies that recognize MSCRAMM®'s from both coagulase-positive bacteria such as *S. aureus* as well as MSCRAMM®'s from coagulase-negative bacteria, such as *S. epidermidis* and *S. hemolyticus*.

It is also an object of the present invention to identify and isolate MSCRAMM®'s from staphylococcal bacteria, as well as their active regions such as the A domain, which can be used to generate monoclonal and polyclonal antibodies that will be cross-reactive against both coagulase-positive and coagulase-negative staphylococci.

It is still further an object of the present invention to provide isolated antibodies that can recognize the A domain of surface proteins such as the DgsK protein from coagulase-negative staphylococci and at the same time recognize surface proteins such as the SasA protein from *Staphylococcus aureus*.

It is yet another object of the present invention to utilize the isolated proteins, A domains and antibodies of the invention to produce vaccines useful in the treatment or prevention of staphylococcal infections, and to provide methods wherein the vaccines and antibodies of the invention are used to prevent or treat a staphylococcal infection.

These and other objects are provided by virtue of the present invention which comprises the identification and isolation of surface proteins from one type of staphylococcal bacteria, such as coagulase-negative or coagulase-positive staph, which can give rise to cross-reactive antibodies which can recognize surface proteins of both types of staph and which can thus be utilized in vaccines and methods of treating or preventing a wide range of staphylococcal infections. The present invention also relates to the generation of both polyclonal and monoclonal antibodies from these surface proteins and their use in preventing or treating staphylococcal infections.

These embodiments and other alternatives and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the present specification and/or the references cited herein, all of which are incorporated by reference.

Brief Description of the Drawing Figures

Figure 1 is a depiction of the primary structure of the in silico-predicted proteins in accordance with the present invention.

Figure 2 shows a Coomassie gel of the purified N-terminal recombinant His-tagged proteins expressing the orfs of the present invention.

Figures 3A-3C show Western blotting of *S. aureus* cell wall extracts showing probing with anti-KesK antibodies (Fig. 3A), anti-KnkA antibodies (Fig. 3B) and anti-DsqA antibodies (Fig. 3C), respectively.

Figures 4A-4B show Dot-blotting and Western immunoblotting of *Lactococcus lactis* expressing *S. aureus* MSCRAMM®s, namely KnkA (Fig. 4A) and KesK (Fig. 4B).

Figures 5A-5D representing the probing of recombinant LPXTG proteins in accordance with the present invention with convalescent sera examining *in vivo* expression, including RrKn and RrKN2 (Fig. 5A), Kesk1 and Kesk2A (Fig. 5B), KnkA (Fig. 5C) and DsqA2 (Fig. 5D).

Figure 6 shows a Western blot analysis demonstrating that rabbit polyclonal antibodies against *S. aureus* SasA cross-react with a protein released from the cell surface of *S. epidermidis* HB as well as the recombinant A-region from DsgK cloned from *S. epidermidis*.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the present invention, there are provided specific surface proteins from coagulase-positive staphylococcal bacteria, such as *S. aureus* as well as from coagulase-negative staph such as *S. epidermidis* and *S. hemolyticus,* including active fragments thereof such as the A domains of these proteins or other epitotic regions which can generate antibodies that recognize the whole protein. In accordance with the invention, the identification and isolation of candidate peptide sequences and proteins was carried out based on some of the common features of the MSCRAMM®s ((Microbial Surface Components Recognizing Adhesive Matrix Molecules) which are in most cases are covalently anchored to the cell wall peptidoglycan. These surface proteins had the following common features which

were utilized in identifying and isolated the sequences of the present invention, namely: (i) an N-terminal signal peptide (approximately 40 residues in length) required for Sec-dependent secretion, (ii) a wall spanning domain either rich in proline and glycine residues or composed of serine and aspartate dipeptide repeats, (iii) an LPXTG motif required for covalent anchoring of the protein to the pentaglycine crossbridge in peptidoglycan, (iv) a hydrophobic membrane-spanning domain followed by (v) several positively charged residues.

In accordance with the invention, by exploiting the whole genome of *S. aureus* in light of the properties as set forth above, at least eight novel open reading frames encoding proteins with secretion and anchorage motifs indicative of MSCRAMMs were identified (i.e. bearing an N-terminal signal peptide and a C-terminal LPXTG motif followed by a hydrophobic domain and a positively charged tail). Table 1 illustrates the list of proteins identified including their distribution among *S. aureus* genomes, their protein size and C-terminal cell wall sorting sequence.

Table 1.

Name	Distribution	Size	C-terminus
EkeS	ENCSJM	2189 aa	**LPNTG**SEEMDLPLKELALITGAALLA**RRRS KKEKES**
DsqA	ENCSJM	~1363-2283 aa	**LPDTG**DSIKQNGLLGGVMTLLVGLGLM**KR KKKKDENDQDD**SQA
KesK	ENCSJM	~909 aa	**LPKTG**ETTSSQSWWGLYALLGMLALFIP**K FRKESK**
KrkN2	ENCSJM (Cowan)	~278 aa	**LPKTG**LTSVDNFISTVAFATLALLGSLSLLLF **KRKESK**
KrkN	ENCSJM	~661 aa	**LPQTG**EESNKDMTLPLMALIALSSIVAFVLP **RKRKN**
RkaS	ENCSJM	~801 aa	**LPKTG**TNQSSSPEAMFVLLAGIGLIATV**RR RKAS**
RrkN	NCSJM	1629 aa	**LPKTG**LESTQKGLIFSSIIGIAGLMLLA**RRRK N**
KnkA	NCSJM	629 aa	**LPKAG**ETIKEHWLPISVIVGAMGVLMIWLS **RRNKLKNK**A

Abbreviations: eMRSA-16; N, 8325; C, COL; S, MSSA; J, N315, M, Mu50.
Six out of eight are conserved in all of the six staphylococcal genomes currently sequenced and the remaining two are present in 5/6 of these genomes.

In accordance with the invention, amino acid and nucleic acid sequences coding for the above proteins were obtained, and these were as follows: Ekes MRSA – SEQ ID NO:1 (DNA sequence); EkeS_MRSA – SEQ ID NO:2 (Protein sequence); DsqA (8325) – SEQ ID NO:3 (DNA sequence); DsqA (8325) – SEQ ID NO:4 (Protein sequence); KesK1 (8325) – SEQ ID NO:5 (DNA sequence); KesK1 (8325) – SEQ ID NO:6 (Protein sequence); KrkN2 (8325) — SEQ ID NO:7 (DNA sequence); KrkN2 (8325) – SEQ ID NO:8 (Protein sequence); KrkN (8325) – SEQ ID NO:9 (DNA sequence); KrkN (8325) – SEQ ID NO:10 (Protein sequence); RkaS (COL) – SEQ ID NO:11 (DNA sequence); RkaS (COL) – SEQ ID NO:12 (Protein sequence); RrkN (8325) – SEQ ID NO:13 (DNA sequence); RrkN (8325) – SEQ ID NO:14 (Protein sequence); KnkA (8325) – SEQ ID NO:15 (DNA sequence); KnkA (8325) – SEQ ID NO:16 (Protein sequence).

In accordance with the present invention, isolated antibodies may be generated from the above proteins or their active regions such as the A domain so as to be able to recognize said proteins and/or said domains. These antibodies may be either monoclonal or polyclonal. If polyclonal antibodies are desired, these may be generated in any of a number of conventional ways well known in the art. In a typical process, the desired surface protein or active region thereof may be injected into a suitable host animal, e.g., a mouse or rabbit, and after a suitable time period, antibodies may be isolated and recovered from the host animal. With regard to monoclonal antibodies, in accordance with the present invention, these may be produced in any number of suitable ways including, e.g., the well known method of Kohler and Milstein, Nature 256:495-497 (1975), or other suitable ways known in the field, such as those methods disclosed in U.S. Pat. Nos. 6,331,415; 5,981,216; 5,807,715; and 4,816,567; Eur. Pat. App. 519,596; and PCT publication WO 00/71585, all of these patent publications incorporated herein by reference. These methods include their preparation as chimeric, humanized, or human monoclonal antibodies in ways that would be well known in this field. Still further, monoclonal antibodies may be prepared from a single chain, such as the light or heavy chains, and in addition may be prepared from active fragments of an

antibody which retain the binding characteristics (e.g., specificity and/or affinity) of the whole antibody. By active fragments is meant an antibody fragment which has the same binding specificity as a complete antibody which binds to the particular surface protein or its homologue from the different type of staph bacteria (i.e., coagulase negative or coagulase-positive), and the term "antibody" as used herein is meant to include said fragments. Additionally, antisera prepared using monoclonal or polyclonal antibodies in accordance with the invention are also contemplated and may be prepared in a number of suitable ways as would be recognized by one skilled in the art.

As indicated above, antibodies to the isolated surface proteins and/or their active regions in accordance with the invention may be prepared in a number of suitable ways that would be well known in the art, such as the well-established Kohler and Milstein method described above which can be utilized to generate monoclonal antibodies. For example, in preliminary steps utilized in such a process, mice may be injected intraperitoneally once a week for a prolonged period with a purified recombinant MSCRAMM® in accordance with the invention or an active portion thereof, followed by a test of blood obtained from the immunized mice to determine reactivity to the purified protein. Following identification of mice reactive to the proteins, lymphocytes isolated from mouse spleens are fused to mouse myeloma cells to produce hybridomas positive for the antibodies against the surface proteins of the invention which are then isolated and cultured, following by purification and isotyping.

In order to generate monoclonal antibodies in accordance with the invention, it is preferred that these be generated using recombinantly prepared MSCRAMM®'s in accordance with the invention, and these recombinants may be generated and isolated using a number of standard methods well known in the art. For example, one such method employs the use of *E. coli* expression vector pQE-30 as an expression vector for cloning and expressing recombinant proteins and peptides. In one preferred method, using PCR, the A domain of the surface protein identified as DgsK or SasA was amplified from the sequences described above and subcloned

into the *E. coli* expression vector PQE-30 (Qiagen), which allows for the expression of a recombinant fusion protein containing six histidine residues. This vector was subsequently transformed into *E. coli* strain ATCC 55151, grown in a 15-liter fermentor to an optical density (OD_{600}) of 0.7 and induced with 0.2 mM isopropyl-1-beta-D galactoside (IPTG) for 4 hours. The cells were harvested using an AG Technologies hollow-fiber assembly (pore size 0.45 µm) and the cell paste frozen at –80° C. Cells were lysed in 1X PBS (10 mL buffer/1 g of cell paste) using 2 passes through the French Press @ 1100psi. Lysed cells were spun down at 17,000rpm for 30 minutes to remove cell debris. Supernatant was passed over a 5-mL HiTrap Chelating (Pharmacia) column charged with 0.1M $NiCl_2$. After loading, the column was washed with 5 column volumes of 10mM Tris, pH 8.0, 100mM NaCl (Buffer A). Protein was eluted using a 0-100% gradient of 10mM Tris, pH 8.0, 100mM NaCl, 200 mM imidazole (Buffer B) over 30 column volumes. SdrGN1N2N3 or SdrGN2N3 eluted at ~13% Buffer B (~26mM imidazole). Absorbance at 280nm was monitored. Fractions containing SdrGN1N2N3 or SdrGN2N3 were dialyzed in 1x PBS.

Next, each protein was then put through an endotoxin removal protocol. Buffers used during this protocol were made endotoxin free by passing over a 5-mL Mono-Q sepharose (Pharmacia) column. Protein was divided evenly between 4x 15mL tubes. The volume of each tube was brought to 9mL with Buffer A. 1mL of 10% Triton X-114 was added to each tube and incubated with rotation for 1 hour at 4°C. Tubes were placed in a 37°C water bath to separate phases. Tubes were spun down at 2,000rpm for 10 minutes and the upper aqueous phase from each tube was collected and the detergent extraction repeated. Aqueous phases from the 2nd extraction were combined and passed over a 5-mL IDA chelating (Sigma) column, charged with 0.1M $NiCl_2$ to remove remaining detergent. The column was washed with 9 column volumes of Buffer A before the protein was eluted with 3 column volumes of Buffer B. The eluant was passed over a 5-mL Detoxigel (Sigma) column and the flow-through collected and reapplied to the column. The flow-through from the second pass was collected and dialyzed in 1x PBS. The

purified product was analyzed for concentration, purity and endotoxin level before administration into the mice.

In the preferred process, monoclonal antibodies in accordance with the present invention may be prepared from the recombinant proteins identified above in the following manner. In this process, *E. coli* expressed and purified recombinant SasA and DsgK proteins were used to generate a panel of murine monoclonal antibodies while the mouse sera was used as a source of polyclonal antibodies. Briefly, a group of Balb/C or SJL mice received a series of subcutaneous immunizations of 1-10 mg of protein in solution or mixed with adjuvant as described below in Table 2.

Table 2. Immunization Schemes

RIMMS

Injection	Day	Amount (µg)	Route	Adjuvant
#1	0	5	Subcutaneous	FCA/RIBI
#2	2	1	Subcutaneous	FCA/RIBI
#3	4	1	Subcutaneous	FCA/RIBI
#4	7	1	Subcutaneous	FCA/RIBI
#5	9	1	Subcutaneous	FCA/RIBI

Conventional

Injection	Day	Amount (µg)	Route	Adjuvant
Primary	0	5	Subcutaneous	FCA
Boost #1	14	1	Intraperitoneal	RIBI
Boost #2	28	1	Intraperitoneal	RIBI
Boost #3	42	1	Intraperitoneal	RIBI

At the time of sacrifice (RIMMS) or seven days after a boost (conventional) serum was collected and titered in ELISA assays against MSCRAMM® proteins or on whole cells (S. *epidermidis* and *S. aureus*). Three days after the final boost, the spleens or lymph nodes were removed, teased into a single cell suspension and the lymphocytes harvested. Lymphocytes were then fused to a P3X63Ag8.653 myeloma cell line (ATCC #CRL-1580). Cell fusion, subsequent plating and feeding were performed according to the Production of Monoclonal Antibodies protocol from Current Protocols in Immunology (Chapter 2, Unit 2.), incorporated herein by reference.

Any clones that were generated from the fusion were then screened for specific anti-SasA antibody production using a standard ELISA assay. Positive clones were expanded and tested further for activity in a whole bacterial cell binding assay by flow cytometry and SasA binding by Biacore analysis. Throughout the Biacore analysis, the flow rate remained constant at 10 ml/min. Prior to the SasA or DgsK injection, test antibody was adsorbed to the chip via RAM-Fc binding. At time 0, SasA or DgsK at a concentration of 30 mg/ml was injected over the chip for 3 min followed by 2 minutes of dissociation. This phase of the analysis measured the relative association and disassociation kinetics of the Mab/SasA or DgsK interaction.

Next, the antibodies prepared as set forth above were tested for binding to whole bacteria. In these tests, bacterial samples *S. aureus* Newman, *S. aureus* 67-0, *S. aureus* 397 (Sal6), *S. aureus* Wood, *S. aureus* 8325-4, methicillin resistant *S. aureus* MRSA 16, *S. epidermidis* ATCC 35984, *S. epidermidis* HB, *S. epidermidis* CN-899 and *S. haemolyticus* ATCC 43253 were collected, washed and incubated with Mab or PBS alone (control) at a concentration of 2 µg/ml after blocking with rabbit IgG (50 mg/ml). Following incubation with antibody, bacterial cells were incubated with Goat-$F_{(ab')2}$-Anti-Mouse-$F_{(ab')2}$-FITC which served as the detection antibody. After antibody labeling, bacterial cells were aspirated through the FACScaliber flow cytometer to analyze fluorescence emission (excitation: 488, emission: 570). For each bacterial strain, 10,000 events were collected and measured. These data indicate that antibodies against *S. aureus* SasA were able to recognize a homologous protein on the surface of coagulase-negative staphylococci. The data support Western blot analysis demonstrating that rabbit polyclonal antibodies against *S. aureus* SasA cross-react with a protein released from the cell surface of *S. epidermidis* HB as well as the recombinant A-region from DsgK cloned from *S. epidermidis* (see Figure 6 and Table 3 below).

Table 3. Polyclonal Sera Reactivity

	New man	67-0	397 (SAL 6)	Wo od 46	8325 -4	MRS A 16	ATC C 3598	HB	CN-899	ATC C 4325

							4			3
Normal Mouse Sera	-	-	-	-	-	-	-	-	-	-
Mouse anti-SasA	+	+	+/-	-	+	+	+	+	+	+

Although production of antibodies using recombinant forms of the surface proteins of the present invention is preferred, antibodies may be generated from natural isolated and purified versions of these proteins or their active regions such as the A domain, and monoclonal or polyclonal antibodies can be generated using these proteins or active regions in the same manner as described above to obtain such antibodies. Still other conventional ways are available to generate the antibodies of the present invention using recombinant or natural purified proteins or their active regions, as would be recognized by one skilled in the art.

As would be recognized by one skilled in the art, the antibodies of the present invention may also be formed into suitable pharmaceutical compositions for administration to a human or animal patient in order to treat or prevent an infection caused by staphylococcal bacteria. Pharmaceutical compositions containing the antibodies of the present invention, or effective fragments thereof, may be formulated in combination with any suitable pharmaceutical vehicle, excipient or carrier that would commonly be used in this art, including such as saline, dextrose, water, glycerol, ethanol, other therapeutic compounds, and combinations thereof. As one skilled in this art would recognize, the particular vehicle, excipient or carrier used will vary depending on the patient and the patient's condition, and a variety of modes of administration would be suitable for the compositions of the invention, as would be recognized by one of ordinary skill in this art. Suitable methods of administering any pharmaceutical composition disclosed in this application include,

but are not limited to, topical, oral, anal, vaginal, intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal and intradermal administration.

For topical administration, the composition is formulated in the form of an ointment, cream, gel, lotion, drops (such as eye drops and ear drops), or solution (such as mouthwash). Wound or surgical dressings, sutures and aerosols may be impregnated with the composition. The composition may contain conventional additives, such as preservatives, solvents to promote penetration, and emollients. Topical formulations may also contain conventional carriers such as cream or ointment bases, ethanol, or oleyl alcohol. Additional forms of antibody compositions, and other information concerning compositions, vaccines, methods and applications with regard to other MSCRAMM®s will generally also be applicable to the present invention involving the aforementioned MSCRAMM®s and their active regions and antibodies thereto, and these other MSCRAMM®s are disclosed, for example, in U.S. patents 5,175,096; 5,320,951; 5,416,021; 5,440,014; 5,571,514; 5,652,217; 5,707,702; 5,789,549; 5,840,846; 5,980,908; 6,086,895; 6,008,341; 6,177,084; 5,851,794 and 6,288,214; all of these patents incorporated herein by reference.

The antibody compositions of the present invention may also be administered with a suitable adjuvant in an amount effective to enhance the immunogenic response. For example, suitable adjuvants may include alum (aluminum phosphate or aluminum hydroxide), which is used widely in humans, and other adjuvants such as saponin and its purified component Quil A, Freund's complete adjuvant, RIBBI adjuvant, and other adjuvants used in research and veterinary applications. Still other chemically defined preparations such as muramyl dipeptide, monophosphoryl lipid A, phospholipid conjugates such as those described by Goodman-Snitkoff *et al. J. Immunol.* 147:410-415 (1991) and incorporated by reference herein, encapsulation of the conjugate within a proteoliposome as described by Miller *et al.*, *J. Exp. Med.* 176:1739-1744 (1992) and incorporated by reference herein, and encapsulation of the protein in lipid

vesicles such as Novasome™ lipid vesicles (Micro Vescular Systems, Inc., Nashua, NH) may also be useful.

In any event, the antibody compositions of the present invention which recognize the proteins or their active regions as set forth above will be useful in methods of preventing or treating staphylococcal infection, and in inhibiting binding of staphylococcal bacteria to host tissue and/or cells. In accordance with the present invention, methods are provided for preventing or treating a staphylococcal infection which comprise administering an effective amount of an antibody to the surface proteins as set forth herein or their active subregions so as to treat or prevent a staphylococcal infection. In addition, these monoclonal antibodies will be useful in impairing the binding of staphylococcal bacteria to host cells

Accordingly, in accordance with the invention, administration of the antibodies of the present invention in any of the conventional ways described above (e.g., topical, parenteral, intramuscular, etc.), and will thus provide an extremely useful method of treating or preventing staphylococcal infections in human or animal patients when an effective amount of the antibody compositions are administered to a human or animal patient. By effective amount is meant that level of use, such as of an antibody titer, that will be sufficient to either prevent adherence of the bacteria, to inhibit binding of staph bacteria to host cells and thus be useful in the treatment or prevention of a staph infection. As would be recognized by one of ordinary skill in this art, the level of antibody titer needed to be effective in treating or preventing staphylococcal infection will vary depending on the nature and condition of the patient, and/or the severity of the pre-existing staphylococcal infection.

In addition to use in methods or treating or preventing a staphylococcal infection, the antibodies of the invention may also be used for the specific detection of staphylococcal proteins, or as research tools. The term "antibodies" as used herein includes monoclonal, polyclonal, chimeric, single chain, bispecific, simianized, and humanized or primatized antibodies as well as Fab fragments, such as those fragments which maintain the binding specificity of the antibodies to the

surface proteins specified above, including the products of an Fab immunoglobulin expression library. Accordingly, the invention contemplates the use of single chains such as the variable heavy and light chains of the antibodies. Generation of any of these types of antibodies or antibody fragments is well known to those skilled in the art. In the present case, antibodies to the surface proteins or their active regions as referred to above can be generated, isolated and/or purified, and then used to treat or protect against staphylococcal infection.

Any of the above described antibodies may be labeled directly with a detectable label for identification and quantification of staph bacteria. Labels for use in immunoassays are generally known to those skilled in the art and include enzymes, radioisotopes, and fluorescent, luminescent and chromogenic substances, including colored particles such as colloidal gold or latex beads. Suitable immunoassays include enzyme-linked immunosorbent assays (ELISA).

Alternatively, the antibody may be labeled indirectly by reaction with labeled substances that have an affinity for immunoglobulin. The antibody may be conjugated with a second substance and detected with a labeled third substance having an affinity for the second substance conjugated to the antibody. For example, the antibody may be conjugated to biotin and the antibody-biotin conjugate detected using labeled avidin or streptavidin. Similarly, the antibody may be conjugated to a hapten and the antibody-hapten conjugate detected using labeled anti-hapten antibody. These and other methods of labeling antibodies and assay conjugates are well known to those skilled in the art.

In accordance with the present invention, there are also provided vaccines for either active or passive immunization designed to treat or protect against staphylococcal infections, and these vaccines may be prepared from the surface proteins or their active regions as set forth above using a number of the conventional vaccine preparation methods well known in this field. In the typical vaccine, an immunogenic amount of a suitable surface protein or active fragment thereof is combined with a suitable pharmaceutically acceptable vehicle, carrier or excipient, and an amount of this vaccine effective to immunize a human or animal

patient may be administered as appropriate. By immunogenic amount it would be understood by one of ordinary skill in this art that this refers to any amount of the protein or active fragment or subregion thereof which is able to raise an immunogenic response in the human or animal patient.

In addition to active vaccines wherein antibodies are generated in the patient by virtue of the introduction or administration of an immunogenic amount of a protein or active fragment in accordance with the present invention, the isolated antibodies of the present invention, or active fragments thereof, may also be utilized in the development of vaccines for passive immunization against staph infections. In such a case, the antibody compositions as described above, namely an effective amount of the antibody and a pharmaceutically acceptable vehicle, carrier or excipient, may be administered as appropriate to a human or animal patient.

Accordingly, in accordance with the invention, the proteins or active fragments thereof may be utilized as active vaccines, and the antibodies of the invention may be used as a passive vaccine which will be useful in providing suitable antibodies to treat or prevent a staphylococcal infection. As would be recognized by one skilled in this art, a vaccine may be packaged for administration in a number of suitable ways, such as by parenteral (i.e., intramuscular, intradermal or subcutaneous) administration or nasopharyngeal (i.e., intranasal) administration. One such mode is where the vaccine is injected intramuscularly, e.g., into the deltoid muscle, however, the particular mode of administration will depend on the nature of the bacterial infection to be dealt with and the condition of the patient. The vaccine is preferably combined with a pharmaceutically acceptable vehicle, carrier or excipient to facilitate administration, and the carrier is usually water or a buffered saline, with or without a preservative. The vaccine may be lyophilized for resuspension at the time of administration or in solution.

In addition, in certain cases, the antibodies of the present invention may be modified as necessary so that, when necessary, they become less immunogenic in the patient to whom it is administered. For example, if the patient is a human, the antibody may be "humanized" by transplanting the complimentarity determining

regions of the hybridoma-derived antibody into a human monoclonal antibody as described, e.g., by Jones *et al.*, *Nature* 321:522-525 (1986) or Tempest *et al. Biotechnology* 9:266-273 (1991) or "veneered" by changing the surface exposed murine framework residues in the immunoglobulin variable regions to mimic a homologous human framework counterpart as described, e.g., by Padlan, Molecular Imm. 28:489-498 (1991), these references incorporated herein by reference. Even further, when so desired, the monoclonal antibodies of the present invention may be administered in conjunction with a suitable antibiotic to further enhance the ability of the present compositions to fight bacterial infections when necessary.

In addition to treating human or animal patients, the present compositions may also be used to halt or prevent infection of a medical device or other biomaterials such as an implant. Medical devices or polymeric biomaterials to be coated with the antibodies, proteins and active fragments described herein include, but are not limited to, staples, sutures, replacement heart valves, cardiac assist devices, hard and soft contact lenses, intraocular lens implants (anterior chamber or posterior chamber), other implants such as corneal inlays, kerato-prostheses, vascular stents, epikeratophalia devices, glaucoma shunts, retinal staples, scleral buckles, dental prostheses, thyroplastic devices, laryngoplastic devices, vascular grafts, soft and hard tissue prostheses including, but not limited to, pumps, electrical devices including stimulators and recorders, auditory prostheses, pacemakers, artificial larynx, dental implants, mammary implants, penile implants, cranio/facial tendons, artificial joints, tendons, ligaments, menisci, and disks, artificial bones, artificial organs including artificial pancreas, artificial hearts, artificial limbs, and heart valves; stents, wires, guide wires, intravenous and central venous catheters, laser and balloon angioplasty devices, vascular and heart devices (tubes, catheters, balloons), ventricular assists, blood dialysis components, blood oxygenators, urethral/ureteral/urinary devices (Foley catheters, stents, tubes and balloons), airway catheters (endotracheal and tracheostomy tubes and cuffs), enteral feeding tubes (including nasogastric, intragastric and jejunal tubes), wound drainage tubes, tubes used to drain the body cavities such as the pleural, peritoneal, cranial, and

pericardial cavities, blood bags, test tubes, blood collection tubes, vacutainers, syringes, needles, pipettes, pipette tips, and blood tubing.

It will be understood by those skilled in the art that the term "coated" or "coating", as used herein, means to apply the antibody or active fragment, or pharmaceutical composition derived therefrom, to a surface of the device, preferably an outer surface that would be exposed to streptococcal bacterial infection. The surface of the device need not be entirely covered by the protein, antibody or active fragment.

The preferred dose for administration of an antibody composition in accordance with the present invention is that amount will be effective in preventing of treating a staphylococcal infection, and one would readily recognize that this amount will vary greatly depending on the nature of the infection and the condition of a patient. As indicated above, an "effective amount" of antibody or pharmaceutical agent to be used in accordance with the invention is intended to mean a nontoxic but sufficient amount of the agent, such that the desired prophylactic or therapeutic effect is produced. As will be pointed out below, the exact amount of the antibody or a particular agent that is required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the condition being treated, the particular carrier or adjuvant being used and its mode of administration, and the like. Accordingly, the "effective amount" of any particular antibody composition will vary based on the particular circumstances, and an appropriate effective amount may be determined in each case of application by one of ordinary skill in the art using only routine experimentation. The dose should be adjusted to suit the individual to whom the composition is administered and will vary with age, weight and metabolism of the individual. The compositions may also contain stabilizers or pharmaceutically acceptable preservatives, such as thimerosal (ethyl(2-mercaptobenzoate-S)mercury sodium salt) (Sigma Chemical Company, St. Louis, MO).

When used with suitable labels or other appropriate detectable biomolecule or chemicals, the monoclonal antibodies described herein are useful for purposes

such as *in vivo* and *in vitro* diagnosis of staphylococcal infections or detection of staphylococcal bacteria. Laboratory research may also be facilitated through use of such antibodies. Various types of labels and methods of conjugating the labels to the antibodies of the invention are well known to those skilled in the art, such as the ones set forth below.

For example, the antibody can be conjugated (directly or via chelation) to a radiolabel such as, but not restricted to, ^{32}P, ^{3}H, ^{14}C, ^{35}S, ^{125}I, or ^{131}I. Detection of a label can be by methods such as scintillation counting, gamma ray spectrometry or autoradiography. Bioluminescent labels, such as derivatives of firefly luciferin, are also useful. The bioluminescent substance is covalently bound to the protein by conventional methods, and the labeled protein is detected when an enzyme, such as luciferase, catalyzes a reaction with ATP causing the bioluminescent molecule to emit photons of light. Fluorogens may also be used to label proteins. Examples of fluorogens include fluorescein and derivatives, phycoerythrin, allo-phycocyanin, phycocyanin, rhodamine, and Texas Red. The fluorogens are generally detected by a fluorescence detector.

The location of a ligand in cells can be determined by labeling an antibody as described above and detecting the label in accordance with methods well known to one skilled in the art, such as immunofluorescence microscopy using procedures such as those described by Warren et al. (*Mol. Cell. Biol.*, 7: 1326-1337, 1987).

As indicated above, the monoclonal antibodies of the present invention, or active portions or fragments thereof, are particularly useful for interfering with the initial physical interaction between a staphylococcal pathogen responsible for infection and a mammalian host, and this interference with the physical interaction may be useful both in treating patients and in preventing or reducing bacteria infection on in-dwelling medical devices to make them safer for use.

In another embodiment of the present invention, a kit which may be useful in isolating and identifying staphylococcal bacteria and infection is provided which comprises the antibodies of the present invention in a suitable form, such as lyophilized in a single vessel which then becomes active by addition of an aqueous

sample suspected of containing the staphylococcal bacteria. Such a kit will typically include a suitable container for housing the antibodies in a suitable form along with a suitable immunodetection reagent which will allow identification of complexes binding to the surface proteins or the antibodies of the invention. In general, these kits may contain an antibody in accordance with the invention and means to identify binding of that antibody when a sample from a patient is introduced to the antibody. For example, a suitable immunodetection reagent may comprise an appropriate detectable signal or label, such as a biotin or enzyme that produces a detectable color, etc., which may be linked to the antibody or utilized in other suitable ways so as to provide a detectable result when the antibody binds to the antigen.

In short, the antibodies of the present invention which recognize and bind to the surface proteins of the invention, or active fragments thereof, will thus be useful in treating a wide variety of staphylococcal infections in human and animal patients and in medical or other in-dwelling devices. In accordance with the invention, because of the nature of these proteins and the fact that they contain epitopes in common with proteins of the other type of staphylococcal bacteria, i.e., a protein from a coagulase-negative staph will raise antibodies that recognize a homologous protein from *S. aureus* and vice versa, the antibodies of the invention will exhibit cross-reactivity and should be effective against a broad range of staphylococcal infections. Accordingly, the present invention provides methods and compositions for improved methods of treating or protecting against a wide range of staphylococcal infections.

EXAMPLES

The following examples are provided which exemplify aspects of the preferred embodiments of the present invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventors to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure,

appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1. Isolation and Sequencing of MSCRAMM's from S. Aureus

Staphylococcus aureus is known to express a class of surface-associated proteins which play important roles in pathogenicity by allowing bacteria to avoid host defenses and by acting as adhesins. These proteins are known as MSCRAMMs (Microbial Surface Components Recognizing Adhesive Matrix Molecules) and in most cases are covalently anchored to the cell wall peptidoglycan. They have several common features: (i) an N-terminal signal peptide (approximately 40 residues in length) required for Sec-dependent secretion, (ii) a wall spanning domain either rich in proline and glycine residues or composed of serine and aspartate dipeptide repeats, (iii) an LPXTG motif required for covalent anchoring of the protein to the pentaglycine crossbridge in peptidoglycan, (iv) a hydrophobic membrane-spanning domain followed by (v) several positively charged residues.

By exploiting the whole genome sequences of *S. aureus*, eight novel open reading frames encoding proteins with secretion and anchorage motifs indicative of MSCRAMMs were identified (i.e. bearing an N-terminal signal peptide and a C-terminal LPXTG motif followed by a hydrophobic domain and a positively charged tail). The following Table illustrates the list of proteins identified including their distribution among *S. aureus* genomes, their protein size and C-terminal cell wall sorting sequence.

Name	Distribution	Size	C-terminus
EkeS	ENCSJM	2189 aa	**LPNTG**SEEMDLPLKELALITGAALLA**RRRS KKEKES**
DsqA	ENCSJM	~1363-2283 aa	**LPDTG**DSIKQNGLLGGVMTLLVGLGLM**KR KKKKDENDQDDSQ**A
KesK	ENCSJM	~909 aa	**LPKTG**ETTSSQSWWGLYALLGMLALFIP**K FRKESK**

KrkN2	ENCSJM (Cowan)	~278 aa	**LPKTG**LTSVDNFISTVAFATLALLGSLSLLLF **KRKESK**
KrkN	ENCSJM	~661 aa	**LPQTG**EESNKDMTLPLMALIALSSIVAFVLP **RKRKN**
RkaS	ENCSJM	~801 aa	**LPKTG**TNQSSSPEAMFVLLAGIGLIATV**RR RKA**S
RrkN	NCSJM	1629 aa	**LPKTG**LESTQKGLIFSSIIGIAGLMLLA**RRRK N**
KnkA	NCSJM	629 aa	**LPKAG**ETIKEHWLPISVIVGAMGVLMIWLS **RRNKLKNKA**

Abbreviations: eMRSA-16; N, 8325; C, COL; S, MSSA; J, N315, M, Mu50.
Six out of eight are conserved in all of the six staphylococcal genomes currently sequenced and the remaining two are present in 5/6 of these genomes.

The following is a list of the DNA and protein sequences:

Ekes MRSA (SEQ ID NO:1)

acaacacagcagagaatagacaaccaggaggaaaacgaaatgaatttgttaaagaaaaataaatatagtattag
aaaatataaagtagggatattctctactttaatcgggacagttttattactttcaaacccaaatggtgcacaagctttaac
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acattaaacgtgcctaataatacagataacaatgattcagcgcgtcatctgactttaaaagaaattcaagaagatgtt
cgtcattcgtctgataagccagagttagttgcgattgctgaagaagcatctaatagaccgaaaaagagaagcagac
gtgctgcgccaacagatcctaatgcaacaccagcagatccaacggctacaccagcagatccaacggcaggaaat
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taccattaaaagaattagcactaattacaggcgcagcattattagctagaagacgttctaaaaaagaaaaagaatc
ataa

EkeS_MRSA (SEQ ID NO:2)

MNLLKKNKYSIRKYKVGIFSTLIGTVLLLSNPNGAQALTTDHNVQGGSNQALPGNS
QNTNADTNRDIVNDSQNTPNAHATDNTSTNQALTNHQNVDVANQVGPAPIQPSA
SPAQNNNNSNANSTATEPAANTNNNLASNNNTLNVPNNTDNNDSARHLTLKEIQE
DVRHSSDKPELVAIAEEASNRPKKRSRRAAPTDPNATPADPTATPADPTAGNGSA
PVAITAPYTPTTDPNANNIGQNAPNEVLSFDDNNIRPSTNRSVPTVTVVDNLPGYTL
INGGKVGVFSHAMVRTSMFDSGDAKNYQAQGNVIALGRIRGNDTNDHGDFNGIEK
TLTVNPNSELIFEFNTMTTKNYQGMTNLIIKNADNDTVIGEKVVAYGPIWRLLKVPE
NVSHLKIQFVPKNDAITDARGIYQLRDGYKYYDFVDSIGLHSGSHVYVERRTMEPT
ATNNKEFTVTTSLKNNGNFGASFNTDDFVYKIQLPEGVEYVNNSLTKDFPSGNSG
VDINDMNVTYDAANRIITIKSTGGGTGNSPARLMPDKILDLKYKLRVNNVPTPRTVT
FNDTLTYKTYSQDFINSPAESHTVSTNPYTIDIIMNKDALQAEVDRRIQQADYTFASL
DIFNDLKRRAQTILDENRNNVPLNKRVSQADIDSLANQMQHTLIRSVDAENAVNRK
VDDMEDLVNQNDELTDEEKQAAIQVIEEHKNEIIGNIGDQTTDDGVTRIKDQGIQTL
SGDTATPVVKPNAKQAIRDKAAKQREIINHTPDATQDEIQDALNQLTTDETDAIDNV
TNATTNADVETAKNNGINTIGAVAPQVTHKQAARDAINQATATKRQQINSNREATQ
EEKNAALNELTQATNHALEQINQATTNDDVDTAKGDGLNAINPIAPVTVVKQAARD
AVSHDAQQHIAEINANPDATQEERQAAIEKVYAAVAVANTNILNANTNADVEQVKT
NAIQGIQAIEPATKVKTDAKNAIDQSAETQHNAIFNNNDATLEEQQAAQQLLDQAVA
TAKQNINAADTNQEVAQAKDQGTQNIVVIQPATQVKTDARNAVNEKAREAITNINA
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KQTATGVLTDLATAKKQEINQNTNATTEEKQVALNQVDQDLATAINNINQADTNAE
VDQAQQLGTKAINAIQPNIVKKPAALAQTNQHYSAKLVEINATPDATDDEKNAAINT
LNQDRQQAIESIKQANTNAEVDQAATVAENNIDAVQVDVVKKQAARDKITAEVAKR
IEAVKQTPNATDEEKQAAVNQINQLKDQAFNQINQNQTNDQVDATTNQAINAIDNV
EAEVVIKPKAIADIEKAVKEKQQQIDNSLDSTDNEKEVALQALAKEKEKALAAIDQA
QTNSQVNQAATNGVSAIKIIQPETKIKPAAREKINQKANELRAQINQDKEATAEERQ
AALDKINDLVAKAMTNITNDRTNQQVNDSTNQALDDIALVTPDHIVRAAARDAVKQ
QYEAKKHEIEQAEHATDEEKQVALNQLANNEKRALQNINQAIANNDVKRVESNGIA

TLKGVEPHIVVKPEAQEAIKASADNQVESIKDTPHATTDELDEANQQINDTLKQGQ
QDIDNTTQDAAVNDVRNQTIKAIEQIKPKVRRKRAALDNIDESNNNQLDAIRNTLDT
TQDERNVAIAALNKIVNAIKNDIAQNKTNAEVDQTEADGNNNIKVILPKVQVKPAAR
QSVSAKAEAQNALIDQSDLSTEEERLAAKHLVEQALNQAIDQINHADKTAQVNQNS
IDAQNIISKIKPATTVKATALQQIQNIATNKINLIKANNEATDEEQNAAIVQVEKELIKA
KQQIAGAVTNADVAYLLHDGKNEIREIEPVINKKATAREQLTTLFNDKKQAIEANVQ
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KTINDDLARVTHLVQNYRKVSDRNKADALKAITALKLQMDEELKTARTNADVDAVL
KRFNVALGDIEAVITEKENSLLRIDNIAQQTYAKFKAIATPEQLAKVKALIDQYVADG
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DsqA (8325) (SEQ ID NO:3)

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DsqA (8325) (SEQ ID NO:4)

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KesK1 (8325) (SEQ ID NO:5)

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KesK1 (8325) (SEQ ID NO:6)

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KrkN2 (8325) (SEQ ID NO:7)

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KrkN2 (8325) (SEQ ID NO:8)

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KrkN (8325) (SEQ ID NO:9)

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KrkN (8325) (SEQ ID NO:10)

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QDSQKDDNKQLPSVEKENDASSESGKDKTPATKPTKGEVESSSTTPTKVVSTTQ
NVAKPTTASSKTTKDVVQTSAGSSEAKDSAPLQKANIKNTNDGHTQSQNNKNTQE
NKAKSLPQTGEESNKDMTLPLMALLALSSIVAFVLPRKRKN

RkaS (COL) (SEQ ID NO:11)

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RkaS (COL) (SEQ ID NO:12)

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SKVTSNAPSNKPSTVVSTKVNETRDVDTQQASTQKPTHTATFKLSNAKTASLSPR
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QGLPLSNQSKGEEMAKAMNAVGYDAMAVGNHEFDFGYDQLKKLEGMLDFPMLS
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FSKKTDFAVTNGGGIRASIAKGKVTRYDLISVLPFGNTIAQIDVKGSDVWTAFEHSL
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MLLGKPAVSEQPAKGQQGSKGSKSGKDTQPIGDDKVMDPAKKPAPGKVVLLLAH
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EAMFVLLAGIGLIATVRRRKAS

RrkN (8325) (SEQ ID NO:13)

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RrkN (8325) (SEQ ID NO:14)

SGKYGKRSMQMRDKKGPVNKRVDFLSNKLNKYSIRKFTVGTASILIGSLMYLGTQ
QEAEAAENNIENPTTLKDNVQSKEVKIEEVTNKDTAPQGVEAKSEVTSNKDTIEHE
PSVKAEDISKKEDTPKEVADVAEVQPKSSVTHNAETPKVRKARSVDEGSFDITRDS
KNVVESTPITIQGKEHFEGYGSVDIQKKPTDLGVSEVTRFNVGNESNGLIGALQLK
NKIDFSKDFNFKVRVANNHQSNTTGADGWGFLFSKGNAEEYLTNGGILGDKGLVN
SGGFKIDTGYIYTSSMDKTEKQAGQGYRGYGAFVKNDSSGNSQMVGENIDKSKT

NFLNYADNSTNTSDGKFHGQRLNDVILTYVASTGKMRAEYAGKTWETSITDLGLS
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PFKKERKFNPDLAPGTEKVTREGQKGEKTITTPTLKNPLTGVIISKGEPKEEITKDPI
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GPVKGDSIVEKEEIPFEKERKFNPDLAPGTEKVTREGQKGEKTITTPTLKNPLTGEII
SKGESKEEITKDPINELTEYGPETITPGHRDEFDPKLPTGEKEEVPGKPGIKNPETG
DVVRPPVDSVTKYGPVKGDSIVEKEEIPFEKERKFNPDLAPGTEKVTREGQKGEK
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PVKGDSIVEKEEIPFKKERKFNPDLAPGTEKVTREGQKGEKTITTPTLKNPLTGEIIS
KGESKEEITKDPINELTEYGPETITPGHRDEFDPKLPTGEKEEVPGKPGIKNPETGD
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DKIVEFGGEKPKDPKGPENPEKPSRPTHPSGPVNPNNPGLSKDRAKPNGPVHSM
DKNDKVKKSKIAKESVANQEKKRAELPKTGLESTQKGLIFSSIIGIAGLMLLARRRK
N

KnkA (8325) (SEQ ID NO:15)

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KnkA (8325) (SEQ ID NO:16)

GRSMLMAKYRGKPFQLYVKLSCSTMMATSIILTNILPYDAQAASEKDTEITKEILSK
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SSHTEMNGQSDIDSKLDQLLKDLNEVSSNVDRGQQSGEDDLNAMKNDMSQTATT
KHGEKDDKNDEAMVNKALEDLDHLNQQIHKSKDASKDTSEDPAVSTTDNNHEVA
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KKYATQSILESIFNKDEAVKILKDIRVDGKTDQQIADQITRHIDQLSLTTSDDLLTSLID
QSQDKSLLISQILQTKLGKAEADKLAKDWTNKGLSNRQIVDQLKKHFASTGDTSSD
DILKAILNNAKDKKQAIETILATRIERQKAKLLADLITKIETDQNKIFNLVKSALNGKAD
DLLNLQKRLNQTKKDIDYILSPIVNRPSLLDRLNKNGKTTDLNKLANLMNQGSDLLD
SIPDIPTPKPEKTLTLGKGNGLLSGLLNADGNVSLPKAGETIKEHWLPISVIVGAMG
VLMIWLSRRNKLKNKA

Primary structure analysis:

A bioinformatic approach was used for primary structure and function prediction (Figure 1). Proteins RrkN and DsqA possessed a similar structural organization to previously described MSCRAMMs. RrkN is similar in structure to the Pls/Aap proteins of *S. aureus* and *S. epidermidis*, respectively. It contains a 200-residue domain at its N-terminus showing 40% identity to Pls and Aap. The C-terminus of the protein is predominantly composed of a 128 residue repeat domain, which varies in the numbers of repeats from strain to strain. These repeats are also present in Pls and Aap. A putative *sar* homolog and *fnbpA* and *fnbpB* lie directly upstream from RrkN on the genome.

DsqA is similar in structural organization to the Sdr family of proteins. It contains a typical A domain followed by a TYYFTDVK motif which is similar to a conserved TYTFTVYVD motif found in all of the Sdr proteins. The function of this motif has yet to be determined. Two 88 residue repeat domains reside in the centre of the protein

followed by a C-terminal SX-repeat motif similar to the SD-repeat motif found in the Sdr proteins. The size of this repeat varies from strain to strain. DsqA neighbors *secY* and *secA* on the genome. A DsqA homolog (>90% identical) is also found in *S. epidermidis*.

KnkA contains no repeat domains in its sequence. Secondary structure prediction analysis indicate that this protein is predominantly composed of alpha-helices.

RkaS contains no repeat domains in its sequence. BLAST analysis indicates that it is similar to a 5' nucleotidase UDP-sugar hydrolase. The gene encoding RkaS lies directly upstream from *orfX*, the insertion site of the *mec* element.

KesK contains two 140 residue repeat domains at the N-terminus of the protein which are 38% identical. Hydropathy plot analysis (Kyte and Doolittle, 1982) indicates that there is a large hydrophilic domain in the center of the protein (residue 500-560).

EkeS contains two 300 residue repeat domains in the center of the protein which are 38% identical. Blast analysis indicates that the N-terminus of the protein (residues 1-1268, bearing both repeats) is 49% identical to FmtB, an LPXTG protein with 17 tandem repeats. FmtB is proposed to be involved indirectly in methicillin resistance as inactivation of *fmtB* abolishes methicillin resistance. This appears to be due to affecting cell wall composition as methicillin sensitivity can be relieved by increasing the production of the cell wall precursor glucosamine-1-phosphate (Komatsuzawa *et al.*, 2000).

KrkN and KrkN2 neighbor each other on the genome.

Expression analysis:

Due to lack of sequence homology with protein databases, a putative function for each of these proteins could not be predicted and hence a molecular approach was taken. Unique regions of four of the *orfs* were expressed in *E. coli* as recombinant his-tagged fusion proteins using the Qiagen pQE-30 expression system. Figure 2. represents a Coomassie stained SDS-PAGE gel of the purified N-terminal his-tag fusion proteins. The recombinant proteins RrkN1, DsqA2, KesK1 and KnkA were used to generate antibodies in rabbits. Western blotting analysis of *S. aureus* cell wall extracts revealed that KesK, KnkA and DsqA are expressed and cell wall-associated (Figure 3). Strain eMRSA-16 represents a *knkA*-negative strain since it lacks the *knkA* gene. An immunoreactive band of 65kDa reacts with the cell wall fraction from both exponential and stationary phase cells of strain 8325-4 (Figure 3, B). The absence of this band in strain eMRSA-16 suggests that it represents the gene product of *knkA*.

Western immunoblotting of the cell wall fraction of strain 8325-4 using anti-KesK antibodies identified a 150kDa immunoreactive band in both exponential and stationary phase cultures. A similar sized immunoreactive protein released from the cell wall fraction of *Lactococcus lactis* expressing full length KesK on an expression plasmid (pKS80) suggests that the 150kDa band represents the *kesK* gene product (data not shown). A *kesK* knockout mutant in *S. aureus* would be required to confirm the size of the cell wall-released KesK protein.

Western immunoblotting of the cell wall fraction of *S. aureus* strain MSSA and eMRSA-16 using anti-DsqA antibodies identified a 130kDa immunoreactive band. Expression levels are higher in stationary phase cells.

Heterologous expression in *Lactococcus lactis*:

Heterologous expression of *S. aureus* surface proteins in *Lactococcus lactis* (*L. lactis*) has previously been used as a tool to study protein function (Sinha *et al.*, 2000). In this study this surrogate system will be used to express each of the in

silico-predicted MSCRAMMs on the surface of *L. lactis* to fish for a function. KesK and KnkA have been cloned into *L. lactis* and shown by dot blotting to be surface expressed (Figure 4). No cross reaction was observed with the negative control (pKS80 plasmid without an insert) indicating that this is a specific reaction. Cell wall and protoplast fractions of *Lactococcus lactis* bearing pKS-KnkA and pKS-KesK were generated by digestion of cells with lysozyme and mutanolysin and used in Western blotting studies using anti-KnkA and anti-KesK antibodies, respectively. Unlike what was observed in *S. aureus*, KnkA was not detected in the cell wall fraction of *L. lactis* but found to be associated with the protoplast fraction. The anchoring motif of KnkA differs from the consensus LPXTG sequence in that it contains an Alanine residue instead of a Threonine (i.e. LPKAG) (Table 1). It has been recently been published that *S. aureus* contains two sortase genes, srtA and srtB (Pallen, 2001). It is possible that this variant form of the LPXTG motif is processed by the second sortase gene, which is absent in *L. lactis*. This would also explain the slight increase in size of the KnkA protein observed in the protoplast fraction, as the cell wall sorting signal has not been cleaved.

KesK was detected in the cell wall fraction of *L. lactis* but migrated at a smaller molecular weight than the KesK protein released from the cell wall of *S. aureus*. The majority of MSCRAMMs expressed on the surface of *L. lactis* are prone to proteolysis during the cell wall extraction procedure (Louise O'Brien, personal communication). Therefore, it is possible that the KesK protein released from the surface of *L. lactis* represents a truncated form of KesK. Shorter digestion times with lysozyme and mutanolysin has been shown to limit the extent of proteolysis.

Expression of in silico-predicted MSCRAMMs in vivo:

Convalescent-phase sera from 33 patients recovering from *S. aureus* infections were tested in their ability to recognize the purified N-terminal his-tag fusion proteins in an ELISA assay. Pooled sera from children and healthy blood donors were used

as negative controls. A positive reaction was taken as a value equal to or greater than twice the value of the negative control. Figures 5A-5D illustrate that all of the proteins were recognized by 27-42% of the patients suggesting that these proteins are expressed *in vivo* and are immunogenic during infection of the host.

References:

Komatsuzawa, H., Ohta, K., Sugai, M., Fujiwara, T., Glanzmann, P., Berger-Bachi, B., Suginaka, H. (2000) Tn551-mediated insertional inactivation of the *fmtB* gene encoding a cell wall-associated protein abolishes methicillin resistance in *Staphylococcus aureus*. J. Antimicrob. Chemother. **45:** 421-31.

Sinha, B., Francois, P., Que, Y.A., Hussain, M., Heilmann, C., Moreillon, P., Lew, D., Krause, K.H., Peters, G., Herrmann, M. (2000) Heterologously expressed *Staphylococcus aureus* fibronectin-binding proteins are sufficient for invasion of host cells.
Infect. Immun. **68:** 6871-6878.

Pallen, M.J., Lam, A.C., Antonio, M., Dunbar, K. (2000) An embarrassment of sortases - a richness of substrates? Trends. Microbiol. **9:** 97-101

Example 2. Isolation and Sequencing of Cross-Reactive Proteins from S. Aureus and from Coagulase-Negative Staphylococci

It has been recently shown that *S. epidermidis* contains surface proteins structurally related to *S. aureus* MSCRAMM® proteins (US 09/386,962). One protein from *S. aureus* is of particular interest since it has a close homologue in *S. epidermidis*. The protein is called DsqA or SasA (*S. aureus*) and DgsK (*S. epidermidis*). They are characterized by a typical "A" domain of approximately 500 amino acid residues,

followed by two B repeats of 88 residues that are ~40% identical, and a unique SXSX dipeptide repeat that can vary in length depending on the strain. Contained within the A domain of the *S. aureus* DsqA/SasA is a 180 residue region that has ~40% identity to a similar sized domain within region A of *S. aureus* proteins RrkN, Pls and *S. epidermidis* protein Aap The A regions of the DsqA/SasA and DgsK proteins are 46 % identical at the amino acid level, the BB repeats are 50% identical. Active and passive immunization strategies that include; vaccines, polyclonal and monoclonal antibodies recognizing both *S. aureus* and coagulase-negative staphylococcal proteins are the subject of this invention.

Specific Examples of Antibodies that Cross-React with Coagulase-Negative Staphylococci and *S. aureus*.

Coagulase-negative staphylococcal DgsK A-Domain:

Amino Acid Sequence (SEQ ID NO:17)

ASETPITSEISSNSETVANQNSTTIKNSQKETVNSTSLESNHSNSTNKQMSSEVTN
TAQSSEKAGISQQSSETSNQSSKLNTYASTDHVESTTINNDNTAQQDQNKSSNVT
SKSTQSNTSSSEKNISSNLTQSIETKATDSLATSEARTSTNQISNLTSTSTSNQSSP
TSFANLRTFSRFTVLNTMAAPTTTSTTTTSSLTSNSVVVNKDNFNEHMNLSGSATY
DPKTGIATLTPDAYSQKGAISLNTRLDSNRSFRFIGKVNLGNRYEGYSPDGVAGGD
GIGFAFSPGPLGQIGKEGAAVGIGGLNNAFGFKLDTYHNTSTPRSDAKAKADPRN
VGGGGAFGAFVSTDRNGMATTEESTAAKLNVQPTDNSFQDFVIDYNGDTKVMTV
TYAGQTFTRNLTDWIKNSGGTTFSLSMTASTGGAKNLQQVQFGTFEYTESAVAKV
RYVDANTGKDIIPPKTIAGEVDGTVNIDKQLNNFKNLGYSYVGTDALKAPNYTETSG
TPTLKLTNSSQTVIYKFKDVQ

***S. aureus* SasA A-domain:**

Amino Acid Sequence (SEQ ID NO:18)

ASDAPLTSELNTQSETVGNQNSTTIEASTSTADSTSVTKNSSSVQTSNSDTVSSEK
SEKVTSTTNSTSNQQEKLTSTSESTSSKNTTSSSDTKSVASTSSTEQPINTSTNQS
TASNNTSQSTTPSSVNLNKTSTTSTSTAPVKLRTFSRLAMSTFASAATTTAVTANTI
TVNKDNLKQYMTTSGNATYDQSTGIVTLTQDAYSQKGAITLGTRIDSNKSFHFSGK
VNLGNKYEGHGNGGDGIGFAFSPGVLGETGLNGAAVGIGGLSNAFGFKLDTYHNT
SKPNSAAKANADPSNVAGGGAFGAFVTTDSYGVATTYTSSSTADNAAKLNVQPT
NNTFQDFDINYNGDTKVMTVKYAGQTWTRNISDWIAKSGTTNFSLSMTASTGGAT
NLQQVQFGTFEYTESAVTQVRYVDVTTGKDIIPPKTYSGNVDQVVTIDNQQSALTA
KGYNYTSVDSSYASTYNDTNKTVKMTNAGQSVTYYFTDVV

The entire sequence of the Aap protein and the DNA coding therefor (with an indication of the presence of the A domain) is shown below:

***S. epidermidis* Aap Protein (A-domain underlined)** (SEQ ID NO:19)

MGKRRQGPINKKVDFLPNKLNKYSIRKFTVGTASILLGSTLIFGSSSHEAKAAEEKQ
VDPITQANQNDSSERSLENTNQPTVNNEAPQMSSTLQAEEGSNAEAPQSEPTKA
EEGGNAEAAQSEPTKAEEGGNAEAPQSEPTKAEEGGNAEAAQSEPTKTEEGSNV
KAAQSEPTKAEEGSNAEAPQSEPTKTEEGSNAKAAQSEPTKAEEGGNAEAAQSE
PTKTEEGSNAEAPQSEPTKAEEGGNAEAPQSEPTKTEEGGNAEAPNVPTIKANSD
NDTQTQFSEAPTRNDLARKEDIPAVSKNEELQSSQPNTDSKIEPTTSEPVNLNYSS
PFMSLLSMPADSSSNNTKNTIDIPPTTVKGRDNYDFYGRVDIESNPTDLNATNLTR
YNYGQPPGTTTAGAVQFKNQVSFDKDFDFNIRVANNRQSNTTGADGWGFMFSK
KDGDDFLKNGGILREKGTPSAAGFRIDTGYYNNDPLDKIQKQAGQGYRGYGTFVK
NDSQGNTSKVGSGTPSTDFLNYADNTTNDLDGKFHGQKLNNVNLKYNASNQTFT
ATYAGKTWTATLSELGLSPTDSYNFLVTSSQYGNGNSGTYASGVMRADLDGATL
TYTPKAVDGDPIISTKEIPFNKKREFDPNLAPGTEKVVQKGEPGIETTTTPTYVNPN
TGEKVGEGEPTEKITKQPVDEIVHYGGEEIKPGHKDEFDPNAPKGSQTTQPGKPG
VKNPDTGEVVTPPVDDVTKYGPVDGDPITSTEEIPFDKKREFNPDLKPGEERVKQ
KGEPGTKTITTPTTKNPLTGEKVGEGEPTEKITKQPVDEITEYGGEEIKPGHKDEFD
PNAPKGSQEDVPGKPGVKNPGTGEVVTPPVDDVTKYGPVDGDPITSTEEIPFDKK
REFNPDLKPGEERVKQKGEPGTKTITTPTTKNPLTGEKVGEGEPTEKITKQPVDEI
VHYGGEQIPQGHKDEFDPNAPVDSKTEVPGKPGVKNPDTGEVVTPPVDDVTKYG
PVDGDSITSTEEIPFDKKREFDPNLAPGTEKVVQKGEPGTKTITTPTTKNPLTGEKV
GEGKSTEKVTKQPVDEIVEYGPTKAEPGKPAEPGKPAEPGKPAEPGKPAEPGTPAEPGKPA
EPGTPAEPGKPAEPGKPAEPGKPAEPGKPAEPGTPAEPGTPAEPGKPAEPGTPA
EPGKPAEPGTPAEPGKPAESGKPVEPGTPAQSGAPEQPNRSMHSTDNKNQLPD
TGENRQANEGTLVGSLLAIVGSLFIFGRRKKGNEK

***S. epidermidis* aap DNA** (SEQ ID NO:20)

atgggcaaac gtagacaagg tcctattaat aaaaaagtgg

atttttacc taacaaatta aacaagtatt ctataagaaa attcactgtt ggtacggcct
caatattact tggttcgaca cttatttttg gaagtagtag ccatgaagcg aaagctgcag
aagaaaaaca agttgatcca attacacaag ctaatcaaaa tgatagtagt gaaagatcac
ttgaaaacac aaatcaacct actgtaaaca atgaagcacc acagatgtct tctacattgc
aagcagaaga aggaagcaat gcagaagcac ctcaatctga gccaacgaag gcagaagaag
gaggcaatgc agaagcagct caatctgagc caacgaaggc agaagaagga ggcaatgcag
aagcacctca atctgagcca acgaaggcag aagaaggagg caatgcagaa gcagctcaat
ctgagccaac gaagacagaa gaaggaagca acgtaaaagc agctcaatct gagccaacga
aggcagaaga aggaagcaat gcagaagcac ctcaatctga gccaacgaag acagaagaag
gaagcaacgc aaaagcagct caatctgagc caacgaaggc agaagaagga ggcaatgcag
aagcagctca atctgagcca acgaagacag aagaaggaag caatgcagaa gcacctcaat
ctgagccaac gaaggcagaa gaaggaggca atgcagaagc acctcaatct gagccaacga
agacagaaga aggaggcaat gcagaagcac cgaatgttcc aactatcaaa gctaattcag
ataatgatac acaaacacaa ttttcagaag cccctacaag aaatgaccta gctagaaaag
aagatatccc tgctgtttct aaaaacgagg aattacaatc atcacaacca aacactgaca
gtaaaataga acctacaact tcagaacctg tgaatttaaa ttatagttct ccgtttatgt
ccttattaag catgcctgct gatagttcat ccaataacac taaaaataca atagatatac
cgccaactac ggttaaaggt agagataatt acgattttta cggtagagta gatatcgaaa
gtaatcctac agatttaaat gcgacaaatt taacgagata taattatgga cagccacctg
gtacaacaac agctggtgca gttcaattta aaaatcaagt tagttttgat aaagatttcg
actttaacat tagagtagca aacaatcgtc aaagtaatac aactggtgca gatggttggg
gctttatgtt cagcaagaaa gatggggatg atttcctaaa aaacggtggt atcttacgtg
aaaaaggtac acctagtgca gctggtttca gaattgatac aggatattat aataacgatc
cattagataa aatacagaaa caagctggtc aaggctatag agggtatggg acatttgtta
aaaatgactc ccaaggtaat acttctaaag taggatcagg tactccatca acagattttc
ttaactacgc agataatact actaatgatt tagatggtaa attccatggt caaaaattaa
ataatgttaa tttgaaatat aatgcttcaa atcaaacttt tacagctact tatgctggta
aaacttggac ggctacgtta tctgaattag gattgagtcc aactgatagt tacaattttt
tagttacatc aagtcaatat ggaaatggta atagtggtac atacgcaagt ggcgttatga
gagctgattt agatggtgca acattgacat acactcctaa agcagtcgat ggagatccaa

ttatatcaac taaggaaata ccatttaata agaaacgtga atttgatcca aacttagccc caggtacaga aaaagtagtc caaaaaggtg aaccaggaat tgaaacaaca acaacaccaa cttatgtcaa tcctaataca ggagaaaaag ttggcgaagg tgaaccaaca gaaaaaataa caaaacaacc agtggatgaa atcgttcatt atggtggcga agaaatcaag ccaggccata aggatgaatt tgatccaaat gcaccgaaag gtagtcaaac aacgcaacca ggtaagccgg gggttaaaaa tcctgataca ggcgaagtag ttactccacc tgtggatgat gtgacaaaat atggtccagt tgatggagat ccgatcacgt caacggaaga aattccattc gacaagaaac gtgaattcaa tcctgattta aaaccaggtg aagagcgtgt taaacaaaaa ggtgaaccag gaacaaaaac aattacaaca ccaacaacta agaacccatt aacaggggaa aaagttggcg aaggtgaacc aacagaaaaa ataacaaaac aaccagtaga tgaaatcaca gaatatggtg gcgaagaaat caagccaggc cataaggatg aatttgatcc aaatgcaccg aaaggtagcc aagaggacgt tccaggtaaa ccaggagtta aaaaccctgg aacaggcgaa gtagtcacac caccagtgga tgatgtgaca aaatatggtc cagttgatgg agatccgatc acgtcaacgg aagaaattcc attcgacaag aaacgtgaat tcaatcctga tttaaaacca ggtgaagagc gcgttaaaca gaaaggtgaa ccaggaacaa aaacaattac aacgccaaca actaagaacc cattaacagg agaaaaagtt ggcgaaggtg aaccaacaga aaaaataaca aaacaaccag tggatgagat tgttcattat ggtggtgaac aaataccaca aggtcataaa gatgaatttg atccaaatgc acctgtagat agtaaaactg aagttccagg taaaccagga gttaaaaatc ctgatacagg tgaagttgtt accccaccag tggatgatgt gacaaaatat ggtccagttg atggagattc gattacgtca acggaagaaa ttccgtttga taaaaaacgc gaatttgatc caaacttagc gccaggtaca gagaaagtcg ttcaaaaagg tgaaccagga acaaaaacaa ttacaacgcc aacaactaag aacccattaa caggagaaaa agttggcgaa ggtaaatcaa cagaaaaagt cactaaacaa cctgttgacg aaattgttga gtatggtcca acaaaagcag aaccaggtaa accagcggaa ccaggtaaac cagcggaacc aggtaaacca gcggaaccag gtacgccagc agaaccaggt aaaccagcgg aaccaggtac gccagcagaa ccaggtaaac cagcggaacc aggtaaacca gcggaaccag gtaaaccagc ggaaccaggt aaaccagcgg aaccaggtac gccagcagaa ccaggtacgc cagcagaacc aggtaaacca gcggaaccag gtacgccagc agaaccaggt aaaccagcgg aaccaggtac gccagcagaa ccaggtaaac cagcggaatc aggtaaacca gtggaaccag gtacgccagc acaatcaggt gcaccagaac aaccaaatag atcaatgcat tcaacagata ataaaaatca attacctgat acaggtgaaa

atcgtcaagc taatgaggga actttagtcg gatctctatt agcaattgtc ggatcattgt tcatatttgg tcgtcgtaaa aaaggtaatg aaaaataatt tcatataaaa actttctgcc attaa

A-Domain from *S. epidermidis* Aap (amino acids 55-600) (SEQ ID NO:21)

^{55}EKQVDPITQANQNDSSERSLENTNQPTVNNEAPQMSSTLQAEEGSNAEAPQSE PTKAEEGGNAEAAQSEPTKAEEGGNAEAPQSEPTKAEEGGNAEAAQSEPTKTEE GSNVKAAQSEPTKAEEGSNAEAPQSEPTKTEEGSNAKAAQSEPTKAEEGGNAEA AQSEPTKTEEGSNAEAPQSEPTKAEEGGNAEAPQSEPTKTEEGGNAEAPNVPTIK ANSDNDTQTQFSEAPTRNDLARKEDIPAVSKNEELQSSQPNTDSKIEPTTSEPVNL NYSSPFMSLLSMPADSSSNNTKNTIDIPPTTVKGRDNYDFYGRVDIESNPTDLNAT NLTRYNYGQPPGTTTAGAVQFKNQVSFDKDFDFNIRVANNRQSNTTGADGWGF MFSKKDGDDFLKNGGILREKGTPSAAGFRIDTGYYNNDPLDKIQKQAGQGYRGYG TFVKNDSQGNTSKVGSGTPSTDFLNYADNTTNDLDGKFHGQKLNNVNLKYNASN QTFTATYAGKTWTATLSELGLSPTDSYNFLVTSSQYGNGNSGTYASGVMRADLD GA^{600}

Protein Production and Purification

Using PCR, the A domain of DgsK or SasA was amplified from the sequences described above and subcloned into the *E. coli* expression vector PQE-30 (Qiagen), which allows for the expression of a recombinant fusion protein containing six histidine residues. This vector was subsequently transformed into the *E. coli* strain ATCC 55151, grown in a 15-liter fermentor to an optical density (OD_{600}) of 0.7 and induced with 0.2 mM isopropyl-1-beta-D galactoside (IPTG) for 4 hours. The cells were harvested using an AG Technologies hollow-fiber assembly (pore size of 0.45 □m) and the cell paste frozen at –80° C. Cells were lysed in 1X PBS (10 mL of buffer/1 g of cell paste) using 2 passes through the French Press @ 1100psi. Lysed cells were spun down at 17,000rpm for 30 minutes to remove cell debris. Supernatant was passed over a 5-mL HiTrap Chelating (Pharmacia) column charged with 0.1M $NiCl_2$. After loading, the column was washed with 5 column

volumes of 10mM Tris, pH 8.0, 100mM NaCl (Buffer A). Protein was eluted using a 0-100% gradient of 10mM Tris, pH 8.0, 100mM NaCl, 200 mM imidazole (Buffer B) over 30 column volumes. SdrGN1N2N3 or SdrGN2N3 eluted at ~13% Buffer B (~26mM imidazole). Absorbance at 280nm was monitored. Fractions containing SdrGN1N2N3 or SdrGN2N3 were dialyzed in 1x PBS.

Each protein was then put through an endotoxin removal protocol. Buffers used during this protocol were made endotoxin free by passing over a 5-mL Mono-Q sepharose (Pharmacia) column. Protein was divided evenly between 4x 15mL tubes. The volume of each tube was brought to 9mL with Buffer A. 1mL of 10% Triton X-114 was added to each tube and incubated with rotation for 1 hour at 4°C. Tubes were placed in a 37°C water bath to separate phases. Tubes were spun down at 2,000rpm for 10 minutes and the upper aqueous phase from each tube was collected and the detergent extraction repeated. Aqueous phases from the 2nd extraction were combined and passed over a 5-mL IDA chelating (Sigma) column, charged with 0.1M $NiCl_2$ to remove remaining detergent. The column was washed with 9 column volumes of Buffer A before the protein was eluted with 3 column volumes of Buffer B. The eluant was passed over a 5-mL Detoxigel (Sigma) column and the flow-through collected and reapplied to the column. The flow-through from the second pass was collected and dialyzed in 1x PBS. The purified product was analyzed for concentration, purity and endotoxin level before administration into the mice.

Monoclonal Antibody Production

E. coli expressed and purified recombinant SasA and DsgK proteins were used to generate a panel of murine monoclonal antibodies while the mouse sera was used as a source of polyclonal antibodies. Briefly, a group of Balb/C or SJL mice received a series of subcutaneous immunizations of 1-10 mg of protein in solution or mixed with adjuvant as described in the Table below.

Immunization Schemes

RIMMS

Injection	Day	Amount (µg)	Route	Adjuvant
#1	0	5	Subcutaneous	FCA/RIBI
#2	2	1	Subcutaneous	FCA/RIBI
#3	4	1	Subcutaneous	FCA/RIBI
#4	7	1	Subcutaneous	FCA/RIBI
#5	9	1	Subcutaneous	FCA/RIBI

Conventional

Injection	Day	Amount (µg)	Route	Adjuvant
Primary	0	5	Subcutaneous	FCA
Boost #1	14	1	Intraperitoneal	RIBI
Boost #2	28	1	Intraperitoneal	RIBI
Boost #3	42	1	Intraperitoneal	RIBI

At the time of sacrifice (RIMMS) or seven days after a boost (conventional) serum was collected and titered in ELISA assays against MSCRAMM® proteins or on whole cells (S. *epidermidis* and *S. aureus*). Three days after the final boost, the spleens or lymph nodes were removed, teased into a single cell suspension and the lymphocytes harvested. The lymphocytes were then fused to a P3X63Ag8.653 myeloma cell line (ATCC #CRL-1580). Cell fusion, subsequent plating and feeding were performed according to the Production of Monoclonal Antibodies protocol from Current Protocols in Immunology (Chapter 2, Unit 2.).

Any clones that were generated from the fusion were then screened for specific anti-SasA antibody production using a standard ELISA assay. Positive clones were expanded and tested further for activity in a whole bacterial cell binding assay by flow cytometry and SasA binding by Biacore analysis.

Biacore Analysis

Throughout the analysis, the flow rate remained constant at 10 ml/min. Prior to the SasA or DgsK injection, test antibody was adsorbed to the chip via RAM-Fc binding. At time 0, SasA or DgsK at a concentration of 30 mg/ml was injected over the chip for 3 min followed by 2 minutes of dissociation. This phase of the analysis

measured the relative association and disassociation kinetics of the Mab / SasA or DgsK interaction.

Binding to Whole Bacteria

Bacterial samples *S. aureus* Newman, *S. aureus* 67-0, *S. aureus* 397 (Sal6), *S. aureus* Wood, *S. aureus* 8325-4, methicillin resistant *S. aureus* MRSA 16, *S. epidermidis* ATCC 35984, *S. epidermidis* HB, *S. epidermidis* CN-899 and *S. haemolyticus* ATCC 43253 were collected, washed and incubated with Mab or PBS alone (control) at a concentration of 2 µg/ml after blocking with rabbit IgG (50 mg/ml). Following incubation with antibody, bacterial cells were incubated with Goat-$F_{(ab')2}$-Anti-Mouse-$F_{(ab')2}$-FITC which served as the detection antibody. After antibody labeling, bacterial cells were aspirated through the FACScaliber flow cytometer to analyze fluorescence emission (excitation: 488, emission: 570). For each bacterial strain, 10,000 events were collected and measured. These data indicate that antibodies against *S. aureus* SasA were able to recognize a homologous protein on the surface of coagulase-negative staphylococci. The data support Western blot analysis demonstrating that rabbit polyclonal antibodies against *S. aureus* SasA cross-react with a protein released from the cell surface of *S. epidermidis* HB as well as the recombinant A-region from DsgK cloned from *S. epidermidis* (see Table below and Figure 6).

Polyclonal Sera Reactivity

	Newman	67-0	397 (SAL6)	Wood 46	8325-4	MRSA 16	ATCC 35984	HB	CN-899	ATCC 43253
Normal Mouse Sera	-	-	-	-	-	-	-	-	-	-
Mouse anti-SasA	+	+	+/-	-	+	+	+	+	+	+

What is claimed is:

1. An isolated antibody which binds to a staphylococcal surface protein selected from the group consisting of SEQ ID NOS. 2, 4, 6, 8, 10, 12, 14, 16, 17, 18, 19 and 21.

2. The antibody according to Claim 1 wherein the antibody is raised against the A domain of the surface protein.

3. The antibody according to Claim 1, wherein the antibody treats or prevents *S. aureus* infection in a human or animal.

4. The antibody according to Claim 1, wherein the antibody is suitable for parenteral, oral, intranasal, subcutaneous, aerosolized or intravenous administration in a human or animal.

5. The antibody according to Claim 1, wherein said antibody is a monoclonal antibody.

6. The antibody according to Claim 1, wherein said antibody is a polyclonal antibody.

7. The antibody according to Claim 5 wherein the monoclonal antibody is of a type selected from the group consisting of murine, chimeric, humanized and human monoclonal antibodies.

8. The antibody according to Claim 5 wherein the antibody is a single chain monoclonal antibody.

9. The antibody according to Claim 1 which comprises an antibody fragment having the same binding specificity of an antibody which binds to a staphylococcal surface protein having the sequence selected from the group consisting of SEQ ID NOS. 2, 4, 6, 8, 10, 12, 14, 16, 17, 18, 19 and 21.

10. The antibody according to Claim 1 that is raised against a protein having an amino acid sequence selected from the group consisting of SEQ ID NOS. 2, 4, 6, 8, 10, 12, 14, 16, 17, 18, 19 and 21.

11. The antibody according to Claim 1 wherein the surface protein has an amino acid sequence encoded by a nucleic acid sequence selected from the group consisting of nucleic acid sequences SEQ ID NOS. 1, 3, 5, 7, 9, 11, 13, 15, 20 and the nucleic acid sequences coding for the A domain of the Aap protein or degenerates thereof.

12. Isolated antisera containing an antibody according to Claim 1.

13. A diagnostic kit comprising an antibody according to Claim 1 and means for detecting binding by that antibody.

14. A diagnostic kit according to Claim 13 wherein said means for detecting binding comprises a detectable label that is linked to said antibody.

15. A method of diagnosing an infection of *S. aureus* comprising adding an antibody according to Claim 1 to a sample suspected of being infected with *S. aureus*, and determining if antibodies have bound to the sample.

16. A pharmaceutical composition for treating or preventing an infection of *S. aureus* comprising an effective amount of the antibody of Claim 1 and a pharmaceutically acceptable vehicle, carrier or excipient.

17. A method of treating or preventing an infection of *S. aureus* comprising administering to a human or animal patient an effective amount of an antibody according to Claim 1.

18. A method of inducing an immunological response comprising administering to a human or animal an immunogenic amount of an isolated protein selected from the group consisting of the amino acid sequences SEQ ID NOS. 2, 4, 6, 8, 10, 12, 14, 16, 17, 18, 19 and 21.

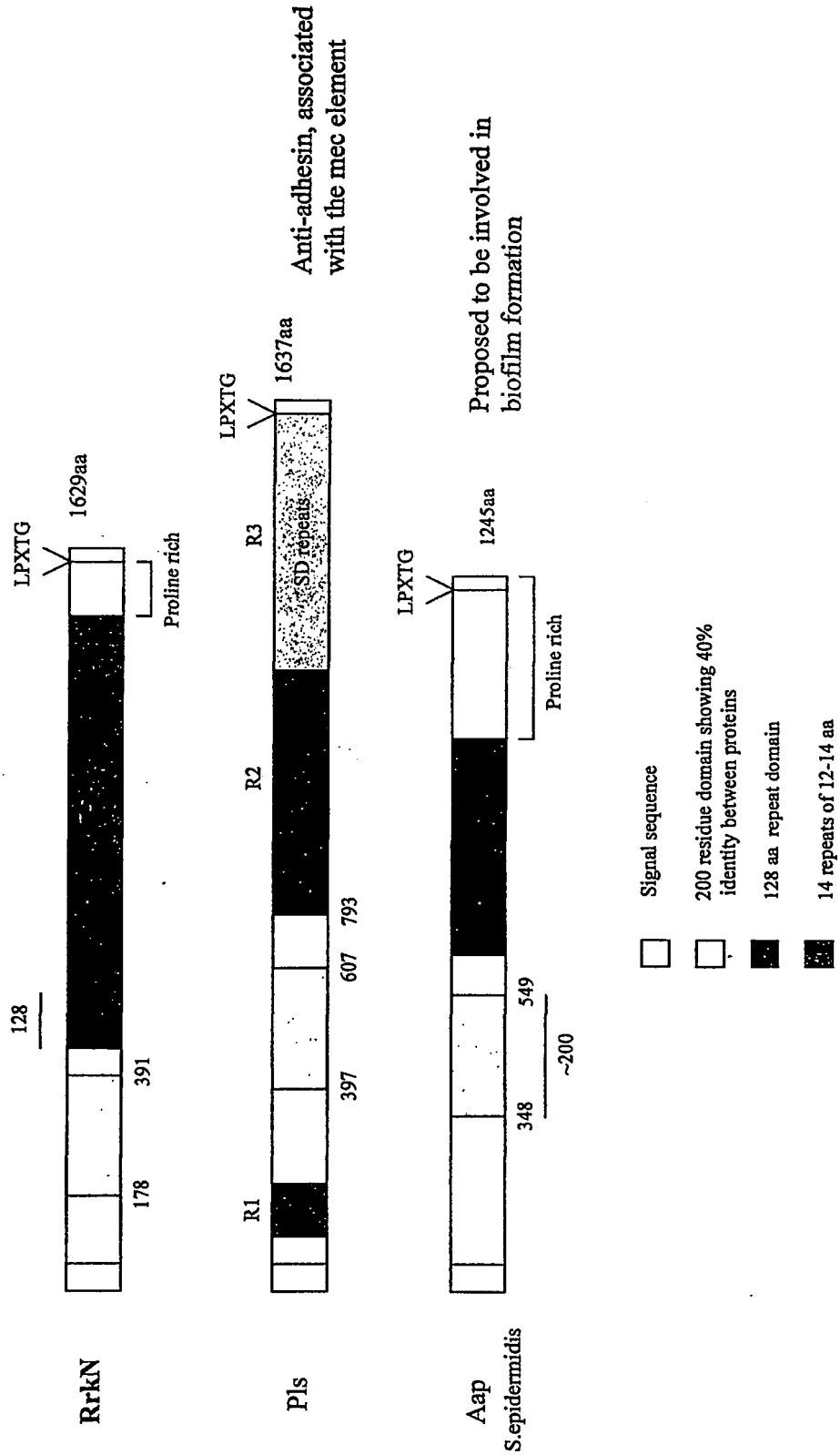
19. An isolated antibody according to Claim 1 that has the ability to bind to an amino acid sequence coded by the nucleic acid sequence of SEQ ID NOS. 1, 3, 5, 7, 9, 11, 13, 15, 20 and the nucleic acid sequences coding for the A domain of the Aap protein or degenerates thereof.

20. An isolated active fragment from the A domain of the DsqA protein.

21. An isolated antibody according to Claim 1 further comprising a physiologically acceptable antibiotic.

22. A vaccine for treating or preventing an infection of *S. aureus* comprising an amount of a protein sequence selected from the group consisting of SEQ ID NOS. 2, 4, 6, 8, 10, 12, 14, 16, 17, 18, 19 and 21 in an amount effective to elicit an immune response, and a pharmaceutically acceptable vehicle, carrier or excipient.

Figure 1. Primary structure of in silico-predicted LPXTG proteins.



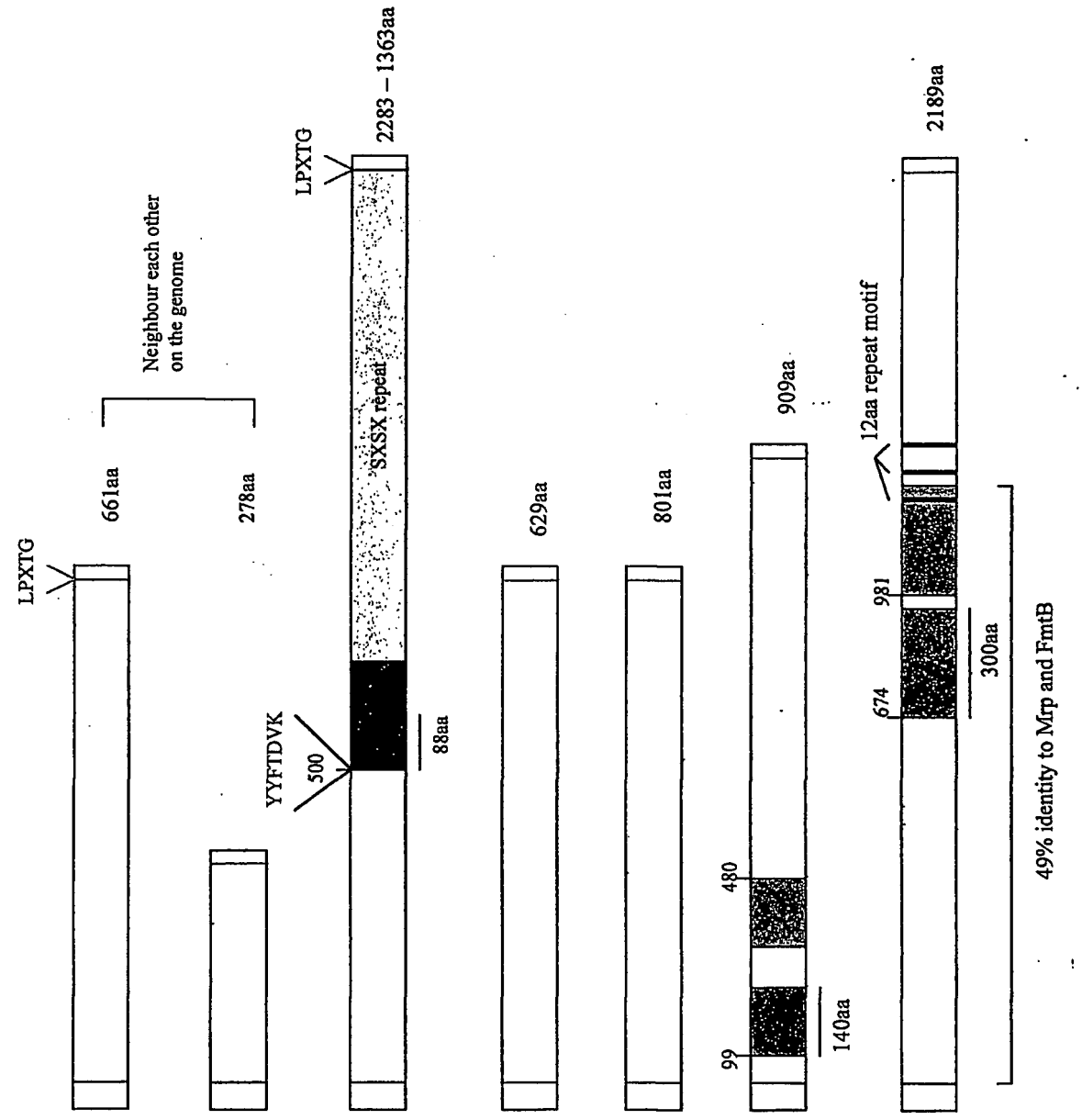
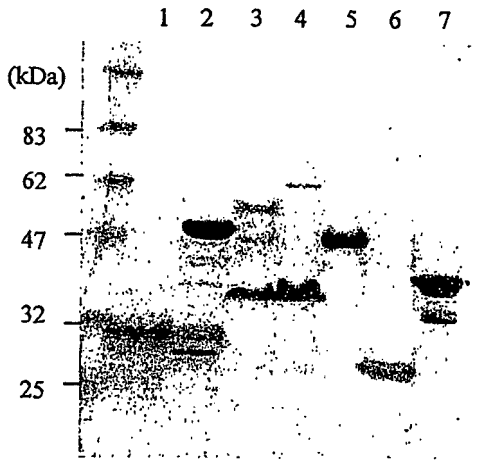


Figure 1 (CONT"D)



		Residues	Predicted MW	Apparent MW
•	**RrkN 1**	60 - 215	19	29
•	**RrkN 2**	60 - 437	45	48
•	**DsqA 1**	54 - 279	27	38
•	**DsqA 2**	54 - 533	58	62
•	**KesK 1**	55 - 335	34	47
•	**KnkA**	39 - 210	20	27
•	**KesK 2**	329 - 591	31	40

Figure 2. Coomassie gel of the purified N-terminal His-tagged fusion proteins.

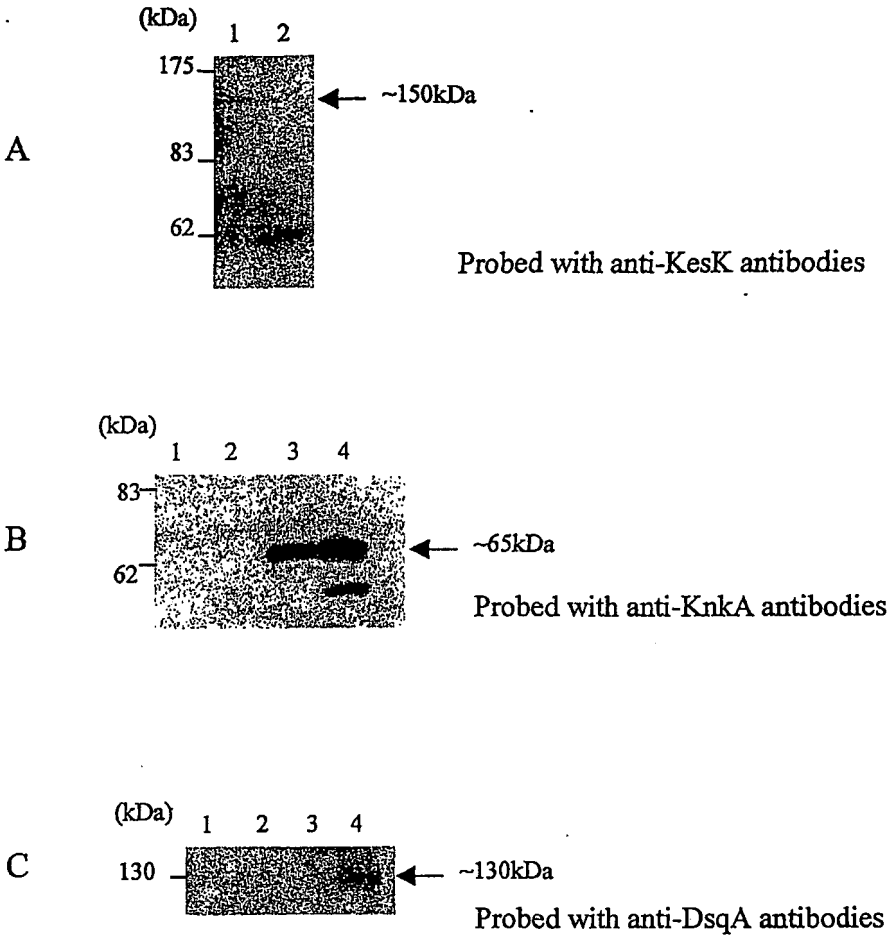


Figure 3. Western blotting of *S.aureus* cell wall extracts. Bacterial cells were standardised to an OD_{600} of 50 units and cell walls were isolated by lysostaphin digestion of stabilised protoplasts.
A. Lane 1, 8325-4 (early exponential phase); lane 2, 8325-4 (stationary phase).
B. Lanes 1 and 2, eMRSA-16 ; lanes 3 and 4, 8325-4; lanes 1 and 3 represent early exponential phase cells and lanes 2 and 4 represent stationary phase cells.
C. Lanes 1 and 2, MSSA ; lanes 3 and 4, eMRSA-16; lanes 1 and 3 represent early exponential phase cells and lanes 2 and 4 represent stationary phase cells.

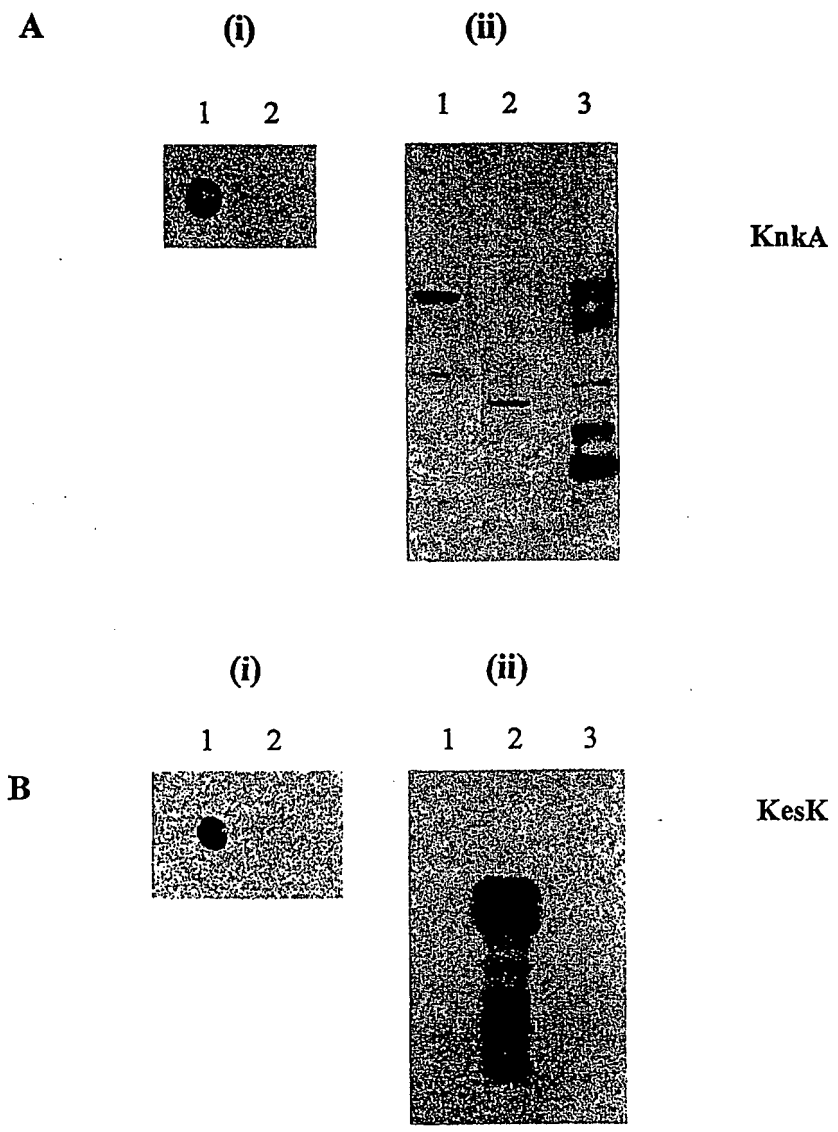


Figure 4. Dot blotting and Western immunoblotting of *Lactococcus lactis* expressing *S.aureus* MSCRAMMs. Full length *knkA* and *kesK* were cloned into the *L.lactis* expression plasmid pKS80 and electroporated into compotent *L.lactis* MG1363 cells. Positive KnkA and KesK expressing clones were detected using dot blotting with anti-KnkA (A) and anti-KesK (B) antibodies, respectively. *L.lactis* bearing pKS80 was used as a negative control. A.(i) lane 1, *L.lactis* pKS-KnkA; lane 2, *L.lactis* pKS80. B. (ii) lane 1, *L.lactis* pKS-KesK; lane 2, *L.lactis* pKS80. Western immunoblotting was used to examine the expression of KesK and KnkA in *S.aureus* and *L.lactis*. A (ii). Lane 1, cell wall extract from exponential phase *S.aureus* strain 8325-4, lane 2, protoplast fraction from *L.lactis* bearing pKS80; lane 3, protoplast fraction from *L.lactis* bearing pKS-KnkA. B. (ii) Lane 1, cell wall extract from exponential phase *S.aureus* strain 8325-4; lane 2, cell wall extract from *L.lactis* bearing pKS-KesK; lane 3, cell wall extract from *L.lactis* bearing pKS80.

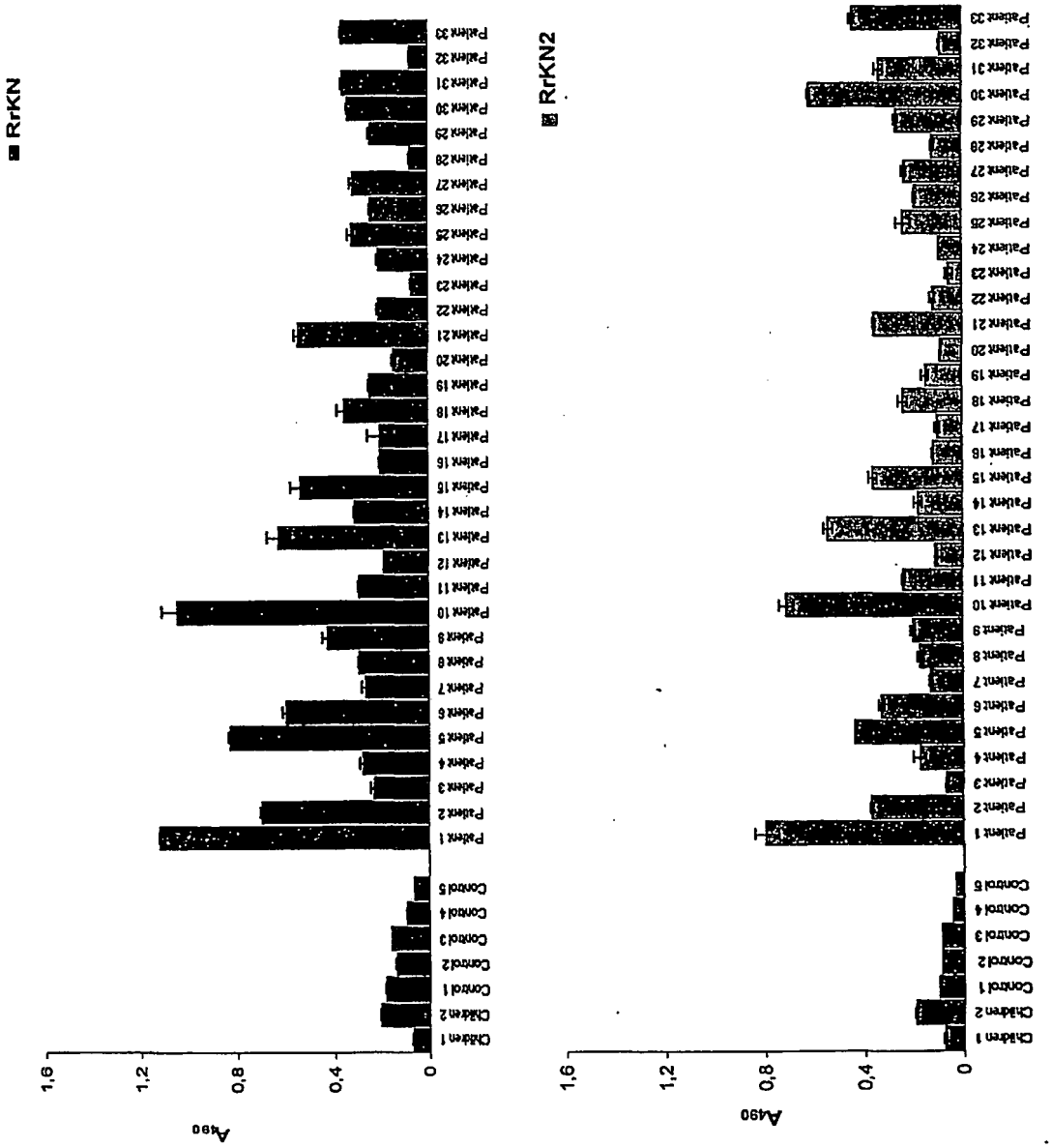


Figure 5A. Probing recombinant LPXTG proteins with convalescent sera to study *in vivo* expression.

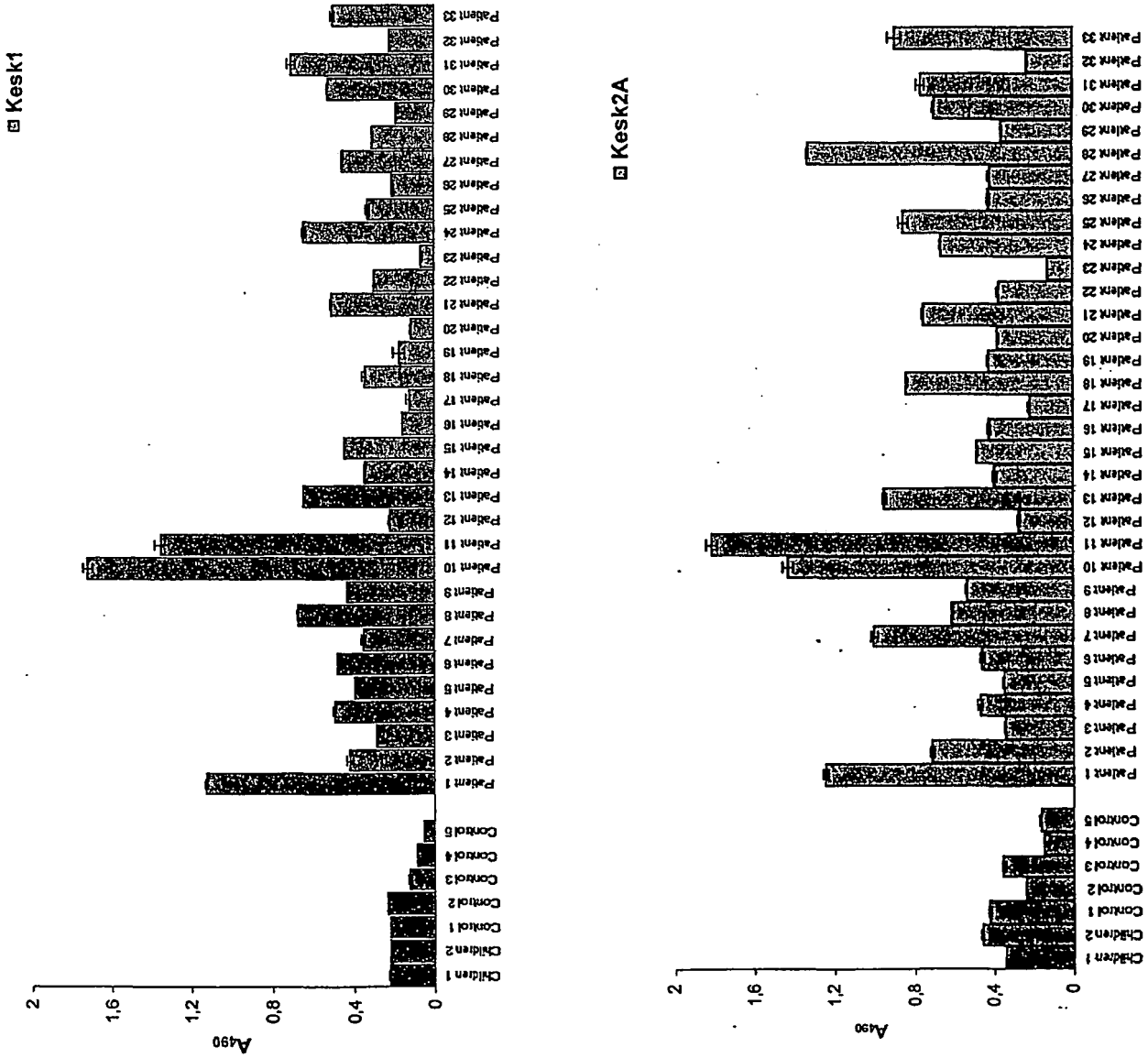

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Figure 5B

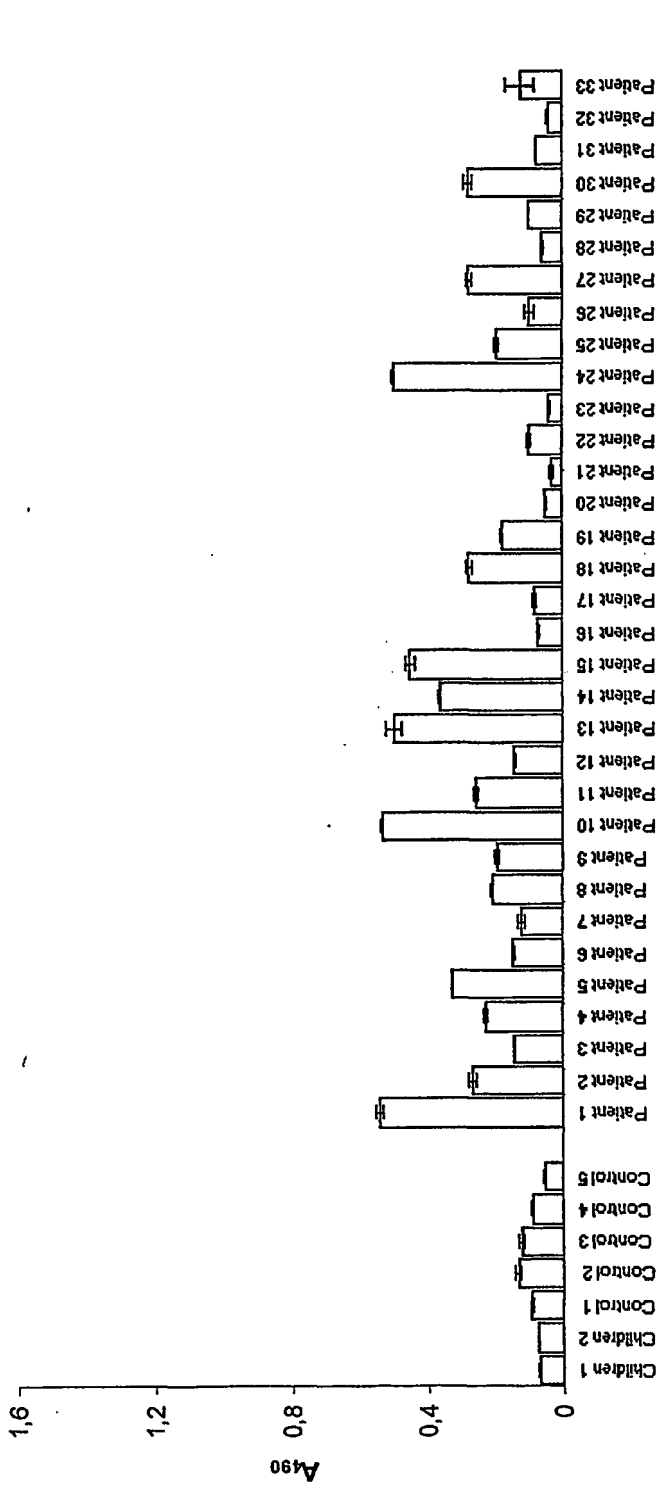
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Figure 5C

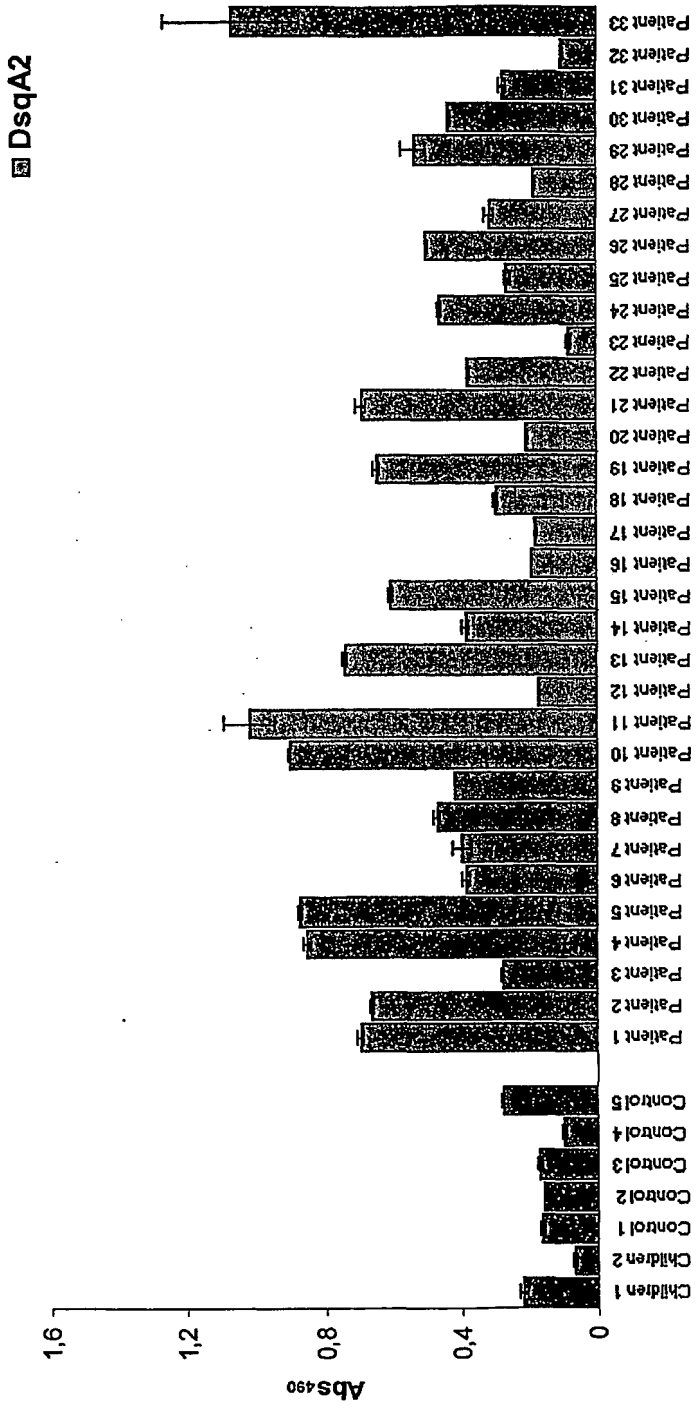
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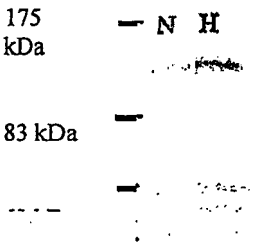
Figure 5D



Western immunoblotting analysis of proteins released from the cell wall of *S. aureus* Newman (N) and *S. epidermidis* HB (H). Probed with rabbit anti-*S. aureus* SasA region A antibodies and goat anti-rabbit conjugated to horseradish peroxidase

Cross reaction of *S. aureus* SasA A-region antibodies with DgsK expressed in *E. coli*. Lane 1, FPLC purified SasA A-region control. Lanes 2, 4 and 6, DgsK A-region expressed from pQE-30 in *E. coli* strain TOPP-3 (induced); lanes 3, 5 and 7, TOPP-3 bearing pQE-30 with *dgsK* insert (uninduced).

FIGURE 6

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Ala Asn Arg Ile Ile Thr Ile Lys Ser Thr Gly Gly Gly Thr Gly Asn
        515                 520                 525
Ser Pro Ala Arg Leu Met Pro Asp Lys Ile Leu Asp Leu Lys Tyr Lys
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Leu Arg Val Asn Asn Val Pro Thr Pro Arg Thr Val Thr Phe Asn Asp
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Thr Leu Thr Tyr Lys Thr Tyr Ser Gln Asp Phe Ile Asn Ser Pro Ala
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Glu Ser His Thr Val Ser Thr Asn Pro Tyr Thr Ile Asp Ile Ile Met
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Arg Val Ser Gln Ala Asp Ile Asp Ser Leu Ala Asn Gln Met Gln His
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Thr Leu Ile Arg Ser Val Asp Ala Glu Asn Ala Val Asn Arg Lys Val
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Asp Asp Met Glu Asp Leu Val Asn Gln Asn Asp Glu Leu Thr Asp Glu
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Glu Lys Gln Ala Ala Ile Gln Val Ile Glu Glu His Lys Asn Glu Ile
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Ile Gly Asn Ile Gly Asp Gln Thr Thr Asp Asp Gly Val Thr Arg Ile
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Lys Asp Gln Gly Ile Gln Thr Leu Ser Gly Asp Thr Ala Thr Pro Val
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Val Lys Pro Asn Ala Lys Gln Ala Ile Arg Asp Lys Ala Ala Lys Gln
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Arg Glu Ile Ile Asn His Thr Pro Asp Ala Thr Gln Asp Glu Ile Gln
755 760 765

Asp Ala Leu Asn Gln Leu Thr Thr Asp Glu Thr Asp Ala Ile Asp Asn
770 775 780

Val Thr Asn Ala Thr Thr Asn Ala Asp Val Glu Thr Ala Lys Asn Asn
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Gly Ile Asn Thr Ile Gly Ala Val Ala Pro Gln Val Thr His Lys Gln
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820 825 830

Ile Asn Ser Asn Arg Glu Ala Thr Gln Glu Glu Lys Asn Ala Ala Leu
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Asn Glu Leu Thr Gln Ala Thr Asn His Ala Leu Glu Gln Ile Asn Gln
850 855 860

Ala Thr Thr Asn Asp Asp Val Asp Thr Ala Lys Gly Asp Gly Leu Asn
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Asp Ala Val Ser His Asp Ala Gln Gln His Ile Ala Glu Ile Asn Ala

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Asn Ala Asp Val Glu Gln Val Lys Thr Asn Ala Ile Gln Gly Ile Gln
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Ala Gly Ala Val Thr Asn Ala Asp Val Ala Tyr Leu Leu His Asp
1865 1870 1875

Gly Lys Asn Glu Ile Arg Glu Ile Glu Pro Val Ile Asn Lys Lys
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Ala Thr Ala Arg Glu Gln Leu Thr Thr Leu Phe Asn Asp Lys Lys
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Gln Ala Ile Glu Ala Asn Val Gln Ala Thr Val Glu Glu Arg Asn
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Gln Ile Asp Gln Asp Arg Ser Asn Ala Gln Val Asp Lys Thr Ala
1940 1945 1950

Thr Leu Asn Leu Gln Thr Ile His Asp Leu Asp Val His Pro Ile
1955 1960 1965

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1970 1975 1980

Val Thr His Leu Val Gln Asn Tyr Arg Lys Val Ser Asp Arg Asn
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Glu Met Phe Lys Ile Met Gly Leu Pro Phe Ile Ser His Ser Leu Val
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Ser Gln Asp Asn Gln Ser Ile Ser Lys Lys Met Thr Gly Tyr Gly Leu
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Leu Gly Glu Thr Gly Leu Asn Gly Ala Ala Val Gly Ile Gly Gly Leu
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Ser Asn Ala Phe Gly Phe Lys Leu Asp Thr Tyr His Asn Thr Ser Lys
    370                 375                 380

Pro Asn Ser Ala Ala Lys Ala Asn Ala Asp Pro Ser Asn Val Ala Gly
385                 390                 395                 400

Gly Gly Ala Phe Gly Ala Phe Val Thr Thr Asp Ser Tyr Gly Val Ala
                405                 410                 415

Thr Thr Tyr Thr Ser Ser Ser Thr Ala Asp Asn Ala Ala Lys Leu Asn
            420                 425                 430

Val Gln Pro Thr Asn Asn Thr Phe Gln Asp Phe Asp Ile Asn Tyr Asn
        435                 440                 445

Gly Asp Thr Lys Val Met Thr Val Lys Tyr Ala Gly Gln Thr Trp Thr
    450                 455                 460

Arg Asn Ile Ser Asp Trp Ile Ala Lys Ser Gly Thr Thr Asn Phe Ser
465                 470                 475                 480

Leu Ser Met Thr Ala Ser Thr Gly Gly Ala Thr Asn Leu Gln Gln Val
                485                 490                 495

Gln Phe Gly Thr Phe Glu Tyr Thr Glu Ser Ala Val Thr Gln Val Arg
            500                 505                 510

Tyr Val Asp Val Thr Thr Gly Lys Asp Ile Ile Pro Pro Lys Thr Tyr
        515                 520                 525
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Ser Gly Asn Val Asp Gln Val Val Thr Ile Asp Asn Gln Gln Ser Ala
    530                 535                 540

Leu Thr Ala Lys Gly Tyr Asn Tyr Thr Ser Val Asp Ser Ser Tyr Ala
545                 550                 555                 560

Ser Thr Tyr Asn Asp Thr Asn Lys Thr Val Lys Met Thr Asn Ala Gly
                565                 570                 575

Gln Ser Val Thr Tyr Tyr Phe Thr Asp Val Lys Ala Pro Thr Val Thr
            580                 585                 590

Val Gly Asn Gln Thr Ile Glu Val Gly Lys Thr Met Asn Pro Ile Val
        595                 600                 605

Leu Thr Thr Thr Asp Asn Gly Thr Gly Thr Val Thr Asn Thr Val Thr
    610                 615                 620

Gly Leu Pro Ser Gly Leu Ser Tyr Asp Ser Ala Thr Asn Ser Ile Ile
625                 630                 635                 640

Gly Thr Pro Thr Lys Ile Gly Gln Ser Thr Val Thr Val Val Ser Thr
                645                 650                 655

Asp Gln Ala Asn Asn Lys Ser Thr Thr Thr Phe Thr Ile Asn Val Val
            660                 665                 670

Asp Thr Thr Ala Pro Thr Val Thr Pro Ile Gly Asp Gln Ser Ser Glu
        675                 680                 685

Val Tyr Ser Pro Ile Ser Pro Ile Lys Ile Ala Thr Gln Asp Asn Ser
    690                 695                 700

Gly Asn Ala Val Thr Asn Thr Val Thr Gly Leu Pro Ser Gly Leu Thr
705                 710                 715                 720

Phe Asp Ser Thr Asn Asn Thr Ile Ser Gly Thr Pro Thr Asn Ile Gly
                725                 730                 735

Thr Ser Thr Ile Ser Ile Val Ser Thr Asp Ala Ser Gly Asn Lys Thr
            740                 745                 750

Thr Thr Thr Phe Lys Tyr Glu Val Thr Arg Asn Ser Met Ser Asp Ser
        755                 760                 765

Val Ser Thr Ser Gly Ser Thr Gln Gln Ser Gln Ser Val Ser Thr Ser
    770                 775                 780

Lys Ala Asp Ser Gln Ser Ala Ser Thr Ser Thr Ser Gly Ser Ile Val
785                 790                 795                 800

Val Ser Thr Ser Ala Ser Thr Ser Lys Ser Thr Ser Val Ser Leu Ser
                805                 810                 815

Asp Ser Val Ser Ala Ser Lys Ser Leu Ser Thr Ser Glu Ser Asn Ser
            820                 825                 830

Val Ser Ser Ser Thr Ser Thr Ser Leu Val Asn Ser Gln Ser Val Ser
        835                 840                 845
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Ser Ser Met Ser Asp Ser Ala Ser Lys Ser Thr Ser Leu Ser Asp Ser
    850                 855                 860

Ile Ser Asn Ser Ser Ser Thr Glu Lys Ser Glu Ser Leu Ser Thr Ser
865                 870                 875                 880

Thr Ser Asp Ser Leu Arg Thr Ser Thr Ser Leu Ser Asp Ser Leu Ser
                885                 890                 895

Met Ser Thr Ser Gly Ser Leu Ser Lys Ser Gln Ser Leu Ser Thr Ser
            900                 905                 910

Ile Ser Gly Ser Ser Ser Thr Ser Ala Ser Leu Ser Asp Ser Thr Ser
        915                 920                 925

Asn Ala Ile Ser Thr Ser Thr Ser Leu Ser Glu Ser Ala Ser Thr Ser
    930                 935                 940

Asp Ser Ile Ser Ile Ser Asn Ser Ile Ala Asn Ser Gln Ser Ala Ser
945                 950                 955                 960

Thr Ser Lys Ser Asp Ser Gln Ser Thr Ser Ile Ser Leu Ser Thr Ser
                965                 970                 975

Asp Ser Lys Ser Met Ser Thr Ser Glu Ser Leu Ser Asp Ser Thr Ser
            980                 985                 990

Thr Ser Gly Ser Val Ser Gly Ser  Leu Ser Ile Ala Ala  Ser Gln Ser
        995                 1000                1005

Val Ser  Thr Ser Thr Ser Asp  Ser Met Ser Thr Ser  Glu Ile Val
    1010                1015                1020

Ser Asp  Ser Ile Ser Thr Ser  Gly Ser Leu Ser Ala  Ser Asp Ser
1025                1030                1035

Lys Ser  Met Ser Val Ser Ser  Ser Met Ser Thr Ser  Gln Ser Gly
    1040                1045                1050

Ser Thr  Ser Glu Ser Leu Ser  Asp Ser Gln Ser Thr  Ser Asp Ser
    1055                1060                1065

Asp Ser  Lys Ser Leu Ser Gln  Ser Thr Ser Gln Ser  Gly Ser Thr
    1070                1075                1080

Ser Thr  Ser Thr Ser Thr Ser  Ala Ser Val Arg Thr  Ser Glu Ser
    1085                1090                1095

Gln Ser  Thr Ser Gly Ser Met  Ser Ala Ser Gln Ser  Asp Ser Met
    1100                1105                1110

Ser Ile  Ser Thr Ser Phe Ser  Asp Ser Thr Ser Asp  Ser Lys Ser
    1115                1120                1125

Ala Ser  Thr Ala Ser Ser Glu  Ser Ile Ser Gln Ser  Ala Ser Thr
    1130                1135                1140

Ser Thr  Ser Gly Ser Val Ser  Thr Ser Thr Ser Leu  Ser Thr Ser
    1145                1150                1155
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Asn Ser Glu Arg Thr Ser Thr Ser Met Ser Asp Ser Thr Ser Leu
1160                1165                1170

Ser Thr Ser Glu Ser Asp Ser Ile Ser Glu Ser Thr Ser Thr Ser
1175                1180                1185

Asp Ser Ile Ser Glu Ala Ile Ser Ala Ser Glu Ser Thr Phe Ile
1190                1195                1200

Ser Leu Ser Glu Ser Asn Ser Thr Ser Asp Ser Glu Ser Gln Ser
1205                1210                1215

Ala Ser Ala Phe Leu Ser Glu Ser Leu Ser Glu Ser Thr Ser Glu
1220                1225                1230

Ser Thr Ser Glu Ser Val Ser Ser Ser Thr Ser Glu Ser Thr Ser
1235                1240                1245

Leu Ser Asp Ser Thr Ser Glu Ser Gly Ser Thr Ser Thr Ser Leu
1250                1255                1260

Ser Asn Ser Thr Ser Gly Ser Thr Ser Ile Ser Thr Ser Thr Ser
1265                1270                1275

Ile Ser Glu Ser Thr Ser Thr Phe Lys Ser Glu Ser Val Ser Thr
1280                1285                1290

Ser Leu Ser Met Ser Thr Ser Thr Ser Leu Ser Asp Ser Thr Ser
1295                1300                1305

Leu Ser Thr Ser Leu Ser Asp Ser Thr Ser Asp Ser Lys Ser Asp
1310                1315                1320

Ser Leu Ser Thr Ser Met Ser Thr Ser Asp Ser Ile Ser Thr Ser
1325                1330                1335

Lys Ser Asp Ser Ile Ser Thr Ser Thr Ser Leu Ser Gly Ser Thr
1340                1345                1350

Ser Glu Ser Glu Ser Asp Ser Thr Ser Ser Ser Glu Ser Lys Ser
1355                1360                1365

Asp Ser Thr Ser Met Ser Ile Ser Met Ser Gln Ser Thr Ser Gly
1370                1375                1380

Ser Thr Ser Thr Ser Thr Ser Thr Ser Leu Ser Asp Ser Thr Ser
1385                1390                1395

Thr Ser Leu Ser Leu Ser Ala Ser Met Asn Gln Ser Gly Val Asp
1400                1405                1410

Ser Asn Ser Ala Ser Gln Ser Ala Ser Asn Ser Thr Ser Thr Ser
1415                1420                1425

Thr Ser Glu Ser Asp Ser Gln Ser Thr Ser Ser Tyr Thr Ser Gln
1430                1435                1440

Ser Thr Ser Gln Ser Glu Ser Thr Ser Thr Ser Thr Ser Leu Ser
1445                1450                1455
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Asp Ser Thr Ser Ile Ser Lys Ser Thr Ser Gln Ser Gly Ser Val
1460 1465 1470

Ser Thr Ser Ala Ser Leu Ser Gly Ser Glu Ser Glu Ser Asp Ser
1475 1480 1485

Gln Ser Ile Ser Thr Ser Ala Ser Glu Ser Thr Ser Glu Ser Ala
1490 1495 1500

Ser Thr Ser Leu Ser Asp Ser Thr Ser Thr Ser Asn Ser Gly Ser
1505 1510 1515

Ala Ser Thr Ser Thr Ser Leu Ser Asn Ser Ala Ser Ala Ser Glu
1520 1525 1530

Ser Asp Leu Ser Ser Thr Ser Leu Ser Asp Ser Thr Ser Ala Ser
1535 1540 1545

Met Gln Ser Ser Glu Ser Asp Ser Gln Ser Thr Ser Ala Ser Leu
1550 1555 1560

Ser Asp Ser Leu Ser Thr Ser Thr Ser Asn Arg Met Ser Thr Ile
1565 1570 1575

Ala Ser Leu Ser Thr Ser Val Ser Thr Ser Glu Ser Gly Ser Thr
1580 1585 1590

Ser Glu Ser Thr Ser Glu Ser Asp Ser Thr Ser Thr Ser Leu Ser
1595 1600 1605

Asp Ser Gln Ser Thr Ser Arg Ser Thr Ser Ala Ser Gly Ser Ala
1610 1615 1620

Ser Thr Ser Thr Ser Thr Ser Asp Ser Arg Ser Thr Ser Ala Ser
1625 1630 1635

Thr Ser Thr Ser Met Arg Thr Ser Thr Ser Asp Ser Gln Ser Met
1640 1645 1650

Ser Leu Ser Thr Ser Thr Ser Thr Ser Met Ser Asp Ser Thr Ser
1655 1660 1665

Leu Ser Asp Ser Val Ser Asp Ser Thr Ser Asp Ser Thr Ser Ala
1670 1675 1680

Ser Thr Ser Gly Ser Met Ser Val Ser Ile Ser Leu Ser Asp Ser
1685 1690 1695

Thr Ser Thr Ser Thr Ser Ala Ser Glu Val Met Ser Ala Ser Ile
1700 1705 1710

Ser Asp Ser Gln Ser Met Ser Glu Ser Val Asn Asp Ser Glu Ser
1715 1720 1725

Val Ser Glu Ser Asn Ser Glu Ser Asp Ser Lys Ser Met Ser Gly
1730 1735 1740

Ser Thr Ser Val Ser Asp Ser Gly Ser Leu Ser Val Ser Thr Ser
1745 1750 1755

Leu Arg Lys Ser Glu Ser Val Ser Glu Ser Ser Ser Leu Ser Cys
1760 1765 1770

Ser Gln Ser Met Ser Asp Ser Val Ser Thr Ser Asp Ser Ser Ser
1775 1780 1785

Leu Ser Val Ser Thr Ser Leu Arg Ser Ser Glu Ser Val Ser Glu
1790 1795 1800

Ser Asp Ser Leu Ser Asp Ser Lys Ser Thr Ser Gly Ser Thr Ser
1805 1810 1815

Thr Ser Thr Ser Gly Ser Leu Ser Thr Ser Thr Ser Leu Ser Gly
1820 1825 1830

Ser Glu Ser Val Ser Glu Ser Thr Ser Leu Ser Asp Ser Ile Ser
1835 1840 1845

Met Ser Asp Ser Thr Ser Thr Ser Asp Ser Asp Ser Leu Ser Gly
1850 1855 1860

Ser Ile Ser Leu Ser Gly Ser Thr Ser Leu Ser Thr Ser Asp Ser
1865 1870 1875

Leu Ser Asp Ser Lys Ser Leu Ser Ser Ser Gln Ser Met Ser Gly
1880 1885 1890

Ser Glu Ser Thr Ser Thr Ser Val Ser Asp Ser Gln Ser Ser Ser
1895 1900 1905

Thr Ser Asn Ser Gln Phe Asp Ser Met Ser Ile Ser Ala Ser Glu
1910 1915 1920

Ser Asp Ser Met Ser Thr Ser Asp Ser Ser Ser Ile Ser Gly Ser
1925 1930 1935

Asn Ser Thr Ser Thr Ser Leu Ser Thr Ser Asp Ser Met Ser Gly
1940 1945 1950

Ser Val Ser Val Ser Thr Ser Thr Ser Leu Ser Asp Ser Ile Ser
1955 1960 1965

Gly Ser Thr Ser Val Ser Asp Ser Ser Ser Thr Ser Thr Ser Thr
1970 1975 1980

Ser Leu Ser Asp Ser Met Ser Gln Ser Gln Ser Thr Ser Thr Ser
1985 1990 1995

Ala Ser Gly Ser Leu Ser Thr Ser Ile Ser Thr Ser Met Ser Met
2000 2005 2010

Ser Ala Ser Thr Ser Ser Ser Gln Ser Thr Ser Val Ser Thr Ser
2015 2020 2025

Leu Ser Thr Ser Asp Ser Ile Ser Asp Ser Thr Ser Ile Ser Ile
2030 2035 2040

Ser Gly Ser Gln Ser Thr Val Glu Ser Glu Ser Thr Ser Asp Ser
2045 2050 2055

Thr Ser Ile Ser Asp Ser Glu Ser Leu Ser Thr Ser Asp Ser Asp
2060 2065 2070

Ser Thr Ser Thr Ser Thr Ser Asp Ser Thr Ser Gly Ser Thr Ser
2075 2080 2085

Thr Ser Ile Ser Glu Ser Leu Ser Thr Ser Gly Ser Gly Ser Thr
2090 2095 2100

Ser Val Ser Asp Ser Thr Ser Met Ser Glu Ser Asn Ser Ser Ser
2105 2110 2115

Val Ser Met Ser Gln Asp Lys Ser Asp Ser Thr Ser Ile Ser Asp
2120 2125 2130

Ser Glu Ser Val Ser Thr Ser Thr Ser Thr Ser Leu Ser Thr Ser
2135 2140 2145

Asp Ser Thr Ser Thr Ser Glu Ser Leu Ser Thr Ser Met Ser Gly
2150 2155 2160

Ser Gln Ser Ile Ser Asp Ser Thr Ser Thr Ser Met Ser Gly Ser
2165 2170 2175

Thr Ser Thr Ser Glu Ser Asn Ser Met His Pro Ser Asp Ser Met
2180 2185 2190

Ser Met His His Thr His Ser Thr Ser Thr Ser Arg Leu Ser Ser
2195 2200 2205

Glu Ala Thr Thr Ser Thr Ser Glu Ser Gln Ser Thr Leu Ser Ala
2210 2215 2220

Thr Ser Glu Val Thr Lys His Asn Gly Thr Pro Ala Gln Ser Glu
2225 2230 2235

Lys Arg Leu Pro Asp Thr Gly Asp Ser Ile Lys Gln Asn Gly Leu
2240 2245 2250

Leu Gly Gly Val Met Thr Leu Leu Val Gly Leu Gly Leu Met Lys
2255 2260 2265

Arg Lys Lys Lys Lys Asp Glu Asn Asp Gln Asp Asp Ser Gln Ala
2270 2275 2280

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<212> DNA
<213> Staphylococcus epidermidis

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agtacactat ttttaattac ttctcaacat caagcacaag cagcagaaaa tacaaatact 180

tcagataaaa tctcggaaaa tcaaaataat aatgcaacta caactcagcc acctaaggat 240

acaaatcaaa cacaacctgc tacgcaacca gcaaacactg cgaaaaacta tcctgcagcg 300

gatgaatcac ttaaagatgc aattaaagat cctgcattag aaaataaaga acatgatata 360
ggtccaagag aacaagtcaa tttccagtta ttagataaaa acaatgaaac gcagtactat 420
cacttttca gcatcaaaga tccagcagat gtgtattaca ctaaaaagaa agcagaagtt 480
gaattagaca tcaatactgc ttcaacatgg aagaagtttg aagtctatga aaacaatcaa 540
aaattgccag tgagacttgt atcatatagt cctgtaccag aagaccatgc ctatattcga 600
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acgagtgaac cgctaaatgt acaaacagga caagaaggta aggttgctga tacagatgta 2100

gctgaaaata gcagcactgc aacaaatcct aaagatgcgt ctgataaagc agatgtgata 2160

gaaccagagt ctgacgtggt taaagatgct gataataata ttgataaaga tgtgcaacat 2220

gatgttgatc atttatccga tatgtcggat aataatcact tcgataaata tgatttaaaa 2280

gaaatggata ctcaaattgc caaagatact gatagaaatg tggataaaga tgccgataat 2340

agcgttggta tgtcatctaa tgtcgatact gataaagact ctaataaaaa taaagacaaa 2400

gtcatacagc tgaatcatat tgccgataaa aataatcata ctggaaaagc agcaaagctt 2460

gacgtagtga aacaaaatta taataataca gacaaagtta ctgacaaaaa aacaactgaa 2520

catctgccga gtgatattca taaaactgta gataaaacag tgaaaacaaa agaaaaagcc 2580

ggcacaccat cgaaagaaaa caaacttagt caatctaaaa tgctaccaaa aactggagaa 2640

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attcctaaat tcagaaaaga atctaaataa 2730

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<212> PRT
<213> Staphylococcus epidermidis

<400> 6

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Lys His His Pro Lys Leu Arg Ser Phe Tyr Ser Ile Arg Lys Ser Thr
20 25 30

Leu Gly Val Ala Ser Val Ile Val Ser Thr Leu Phe Leu Ile Thr Ser
35 40 45

Gln His Gln Ala Gln Ala Ala Glu Asn Thr Asn Thr Ser Asp Lys Ile
50 55 60

Ser Glu Asn Gln Asn Asn Asn Ala Thr Thr Thr Gln Pro Pro Lys Asp
65 70 75 80

Thr Asn Gln Thr Gln Pro Ala Thr Gln Pro Ala Asn Thr Ala Lys Asn
85 90 95

Tyr Pro Ala Ala Asp Glu Ser Leu Lys Asp Ala Ile Lys Asp Pro Ala
100 105 110

Leu Glu Asn Lys Glu His Asp Ile Gly Pro Arg Glu Gln Val Asn Phe
115 120 125

Gln Leu Leu Asp Lys Asn Asn Glu Thr Gln Tyr Tyr His Phe Phe Ser
130 135 140

Ile Lys Asp Pro Ala Asp Val Tyr Tyr Thr Lys Lys Lys Ala Glu Val
145 150 155 160

```
Glu Leu Asp Ile Asn Thr Ala Ser Thr Trp Lys Lys Phe Glu Val Tyr
                165                 170                 175

Glu Asn Asn Gln Lys Leu Pro Val Arg Leu Val Ser Tyr Ser Pro Val
            180                 185                 190

Pro Glu Asp His Ala Tyr Ile Arg Phe Pro Val Ser Asp Gly Thr Gln
        195                 200                 205

Glu Leu Lys Ile Val Ser Ser Thr Gln Ile Asp Asp Gly Glu Glu Thr
    210                 215                 220

Asn Tyr Asp Tyr Thr Lys Leu Val Phe Ala Lys Pro Ile Tyr Asn Asp
225                 230                 235                 240

Pro Ser Leu Val Lys Ser Asp Thr Asn Asp Ala Val Val Thr Asn Asp
                245                 250                 255

Gln Ser Ser Ser Val Ala Ser Asn Gln Thr Asn Thr Asn Thr Ser Asn
            260                 265                 270

Gln Asn Ile Ser Thr Ile Asn Asn Ala Asn Asn Gln Pro Gln Ala Thr
        275                 280                 285

Thr Asn Met Ser Gln Pro Ala Gln Pro Lys Ser Ser Thr Asn Ala Asp
    290                 295                 300

Gln Ala Ser Ser Gln Pro Ala His Glu Thr Asn Ser Asn Gly Asn Thr
305                 310                 315                 320

Asn Asp Lys Thr Asn Glu Ser Ser Asn Gln Ser Asp Val Asn Gln Gln
                325                 330                 335

Tyr Pro Pro Ala Asp Glu Ser Leu Gln Asp Ala Ile Lys Asn Pro Ala
            340                 345                 350

Ile Ile Asp Lys Glu His Thr Ala Asp Asn Trp Arg Pro Ile Asp Phe
        355                 360                 365

Gln Met Lys Asn Asp Lys Gly Glu Arg Gln Phe Tyr His Tyr Ala Ser
    370                 375                 380

Thr Val Glu Pro Ala Thr Val Ile Phe Thr Lys Thr Gly Pro Ile Ile
385                 390                 395                 400

Glu Leu Gly Leu Lys Thr Ala Ser Thr Trp Lys Lys Phe Glu Val Tyr
                405                 410                 415

Glu Gly Asp Lys Lys Leu Pro Val Glu Leu Val Ser Tyr Asp Ser Asp
            420                 425                 430

Lys Asp Tyr Ala Tyr Ile Arg Phe Pro Val Ser Asn Gly Thr Arg Glu
        435                 440                 445

Val Lys Ile Val Ser Ser Ile Glu Tyr Gly Glu Asn Ile His Glu Asp
    450                 455                 460

Tyr Asp Tyr Thr Leu Met Val Phe Ala Gln Pro Ile Thr Asn Asn Pro
465                 470                 475                 480
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Asp Asp Tyr Val Asp Glu Glu Thr Tyr Asn Leu Gln Lys Leu Leu Ala
                485                 490                 495

Pro Tyr His Lys Ala Lys Thr Leu Glu Arg Gln Val Tyr Glu Leu Glu
            500                 505                 510

Lys Leu Gln Glu Lys Leu Pro Glu Lys Tyr Lys Ala Glu Tyr Lys Lys
        515                 520                 525

Lys Leu Asp Gln Thr Arg Val Glu Leu Ala Asp Gln Val Lys Ser Ala
    530                 535                 540

Val Thr Glu Phe Glu Asn Val Thr Pro Thr Asn Asp Gln Leu Thr Asp
545                 550                 555                 560

Leu Gln Glu Ala His Phe Val Val Phe Glu Ser Glu Glu Asn Ser Glu
                565                 570                 575

Ser Val Met Asp Gly Phe Val Glu His Pro Phe Tyr Thr Ala Thr Leu
            580                 585                 590

Asn Gly Gln Lys Tyr Val Val Met Lys Thr Lys Asp Asp Ser Tyr Trp
        595                 600                 605

Lys Asp Leu Ile Val Glu Gly Lys Arg Val Thr Thr Val Ser Lys Asp
    610                 615                 620

Pro Lys Asn Asn Ser Arg Thr Leu Ile Phe Pro Tyr Ile Pro Asp Lys
625                 630                 635                 640

Ala Val Tyr Asn Ala Ile Val Lys Val Val Val Ala Asn Ile Gly Tyr
                645                 650                 655

Glu Gly Gln Tyr His Val Arg Ile Ile Asn Gln Asp Ile Asn Thr Lys
            660                 665                 670

Asp Asp Asp Thr Ser Gln Asn Asn Thr Ser Glu Pro Leu Asn Val Gln
        675                 680                 685

Thr Gly Gln Glu Gly Lys Val Ala Asp Thr Asp Val Ala Glu Asn Ser
    690                 695                 700

Ser Thr Ala Thr Asn Pro Lys Asp Ala Ser Asp Lys Ala Asp Val Ile
705                 710                 715                 720

Glu Pro Glu Ser Asp Val Val Lys Asp Ala Asp Asn Asn Ile Asp Lys
                725                 730                 735

Asp Val Gln His Asp Val Asp His Leu Ser Asp Met Ser Asp Asn Asn
            740                 745                 750

His Phe Asp Lys Tyr Asp Leu Lys Glu Met Asp Thr Gln Ile Ala Lys
        755                 760                 765

Asp Thr Asp Arg Asn Val Asp Lys Asp Ala Asp Asn Ser Val Gly Met
    770                 775                 780

Ser Ser Asn Val Asp Thr Asp Lys Asp Ser Asn Lys Asn Lys Asp Lys
785                 790                 795                 800
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Val Ile Gln Leu Asn His Ile Ala Asp Lys Asn Asn His Thr Gly Lys
805 810 815

Ala Ala Lys Leu Asp Val Val Lys Gln Asn Tyr Asn Asn Thr Asp Lys
820 825 830

Val Thr Asp Lys Lys Thr Thr Glu His Leu Pro Ser Asp Ile His Lys
835 840 845

Thr Val Asp Lys Thr Val Lys Thr Lys Glu Lys Ala Gly Thr Pro Ser
850 855 860

Lys Glu Asn Lys Leu Ser Gln Ser Lys Met Leu Pro Lys Thr Gly Glu
865 870 875 880

Thr Thr Ser Ser Gln Ser Trp Trp Gly Leu Tyr Ala Leu Leu Gly Met
885 890 895

Leu Ala Leu Phe Ile Pro Lys Phe Arg Lys Glu Ser Lys
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<211> 1065
<212> DNA
<213> Staphylococcus epidermidis

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ataggcgcag acagccaaca agtcaatgcg gcaacagaag ctacgaacgc aactaataat 180

caaagcacac aagtttctca agcaacatca caaccaatta atttccaagt gcaaaaagat 240

ggctcttcag agaagtcaca catggatgac tatatgcaac accctggtaa agtaattaaa 300

caaaataata aatattattt ccaaaccgtg ttaaacaatg catcattctg gaaagaatac 360

aaattttaca atgcaaacaa tcaagaatta gcaacaactg ttgttaacga taataaaaaa 420

gcggatacta gaacaatcaa tgttgcagtt gaacctggat ataagagctt aactactaaa 480

gtacatattg tcgtgccaca aattaattac aatcatagat atactacgca tttggaattt 540

gaaaaagcaa ttcctacatt agctgacgca gcaaaaccaa acaatgttaa accggttcaa 600

ccaaaaccag ctcaacctaa aacacctact gagcaaacta aaccagttca acctaaagtt 660

gaaaaagtta aacctactgt aactacaaca agcaaagttg aagacaatca ctctactaaa 720

gttgtaagta ctgacacaac aaaagatcaa actaaaacac aaactgctca tacagttaaa 780

acagcacaaa ctgctcaaga acaaaataaa gttcaaacac ctgttaaaga tgttgcaaca 840

gcgaaatctg aaagcaacaa tcaagctgta agtgataata aatcacaaca aactaacaaa 900

gttacaaaac ataacgaaac gcctaaacaa gcatctaaag ctaaagaatt accaaaaact 960

ggtttaactt cagttgataa ctttattagc acagttgcct tcgcaacact tgcctttta 1020

ggttcattat ctttattact tttcaaaaga aaagaatcta aataa 1065

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<211> 354
<212> PRT
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Glu Gln Arg Ser Ser Ala Met Lys Lys Ile Thr Met Gly Thr Ala Ser
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Ile Ile Leu Gly Ser Leu Val Tyr Ile Gly Ala Asp Ser Gln Gln Val
35 40 45

Asn Ala Ala Thr Glu Ala Thr Asn Ala Thr Asn Asn Gln Ser Thr Gln
50 55 60

Val Ser Gln Ala Thr Ser Gln Pro Ile Asn Phe Gln Val Gln Lys Asp
65 70 75 80

Gly Ser Ser Glu Lys Ser His Met Asp Asp Tyr Met Gln His Pro Gly
85 90 95

Lys Val Ile Lys Gln Asn Asn Lys Tyr Tyr Phe Gln Thr Val Leu Asn
100 105 110

Asn Ala Ser Phe Trp Lys Glu Tyr Lys Phe Tyr Asn Ala Asn Asn Gln
115 120 125

Glu Leu Ala Thr Thr Val Val Asn Asp Asn Lys Lys Ala Asp Thr Arg
130 135 140

Thr Ile Asn Val Ala Val Glu Pro Gly Tyr Lys Ser Leu Thr Thr Lys
145 150 155 160

Val His Ile Val Val Pro Gln Ile Asn Tyr Asn His Arg Tyr Thr Thr
165 170 175

His Leu Glu Phe Glu Lys Ala Ile Pro Thr Leu Ala Asp Ala Ala Lys
180 185 190

Pro Asn Asn Val Lys Pro Val Gln Pro Lys Pro Ala Gln Pro Lys Thr
195 200 205

Pro Thr Glu Gln Thr Lys Pro Val Gln Pro Lys Val Glu Lys Val Lys
210 215 220

Pro Thr Val Thr Thr Thr Ser Lys Val Glu Asp Asn His Ser Thr Lys
225 230 235 240

Val Val Ser Thr Asp Thr Thr Lys Asp Gln Thr Lys Thr Gln Thr Ala
245 250 255

His Thr Val Lys Thr Ala Gln Thr Ala Gln Glu Gln Asn Lys Val Gln

260 265 270

Thr Pro Val Lys Asp Val Ala Thr Ala Lys Ser Glu Ser Asn Asn Gln
275 280 285

Ala Val Ser Asp Asn Lys Ser Gln Gln Thr Asn Lys Val Thr Lys His
290 295 300

Asn Glu Thr Pro Lys Gln Ala Ser Lys Ala Lys Glu Leu Pro Lys Thr
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Ser Lys

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<213> Staphylococcus epidermidis

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Asp Phe Glu Met Lys Lys Lys Asp Gly Thr Gln Gln Phe Tyr His Tyr
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Ala Ser Ser Val Lys Pro Ala Arg Val Ile Phe Thr Asp Ser Lys Pro
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Glu Ile Glu Leu Gly Leu Gln Ser Gly Gln Phe Trp Arg Lys Phe Glu
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Val Tyr Glu Gly Asp Lys Lys Leu Pro Ile Lys Leu Val Ser Tyr Asp
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Thr Val Lys Asp Tyr Ala Tyr Ile Arg Phe Ser Val Ser Asn Gly Thr
225                 230                 235                 240

Lys Ala Val Lys Ile Val Ser Ser Thr His Phe Asn Asn Lys Glu Glu
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Lys Tyr Asp Tyr Thr Leu Met Glu Phe Ala Gln Pro Ile Tyr Asn Ser
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Ala Asp Lys Phe Lys Thr Glu Glu Asp Tyr Lys Ala Glu Lys Leu Leu
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Ala Pro Tyr Lys Lys Ala Lys Thr Leu Glu Arg Gln Val Tyr Glu Leu
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Ala Ile Thr Glu Phe Gln Asn Val Gln Pro Thr Asn Glu Lys Met Thr
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Asp Leu Gln Asp Thr Lys Tyr Val Val Tyr Glu Ser Val Glu Asn Asn
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Glu Ser Met Met Asp Thr Phe Val Lys His Pro Ile Lys Thr Gly Met
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Ala Lys Lys Glu Ala Thr Pro Ala Thr Pro Ser Lys Pro Thr Pro Ser
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Pro Val Glu Lys Glu Ser Gln Lys Gln Asp Ser Gln Lys Asp Asp Asn
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Lys Gln Leu Pro Ser Val Glu Lys Glu Asn Asp Ala Ser Ser Glu Ser
515 520 525

Gly Lys Asp Lys Thr Pro Ala Thr Lys Pro Thr Lys Gly Glu Val Glu
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Ser Ser Ser Thr Thr Pro Thr Lys Val Val Ser Thr Thr Gln Asn Val
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Ala Lys Pro Thr Thr Ala Ser Ser Lys Thr Thr Lys Asp Val Val Gln
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Thr Ser Ala Gly Ser Ser Glu Ala Lys Asp Ser Ala Pro Leu Gln Lys
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Ala Asn Ile Lys Asn Thr Asn Asp Gly His Thr Gln Ser Gln Asn Asn
595 600 605

Lys Asn Thr Gln Glu Asn Lys Ala Lys Ser Leu Pro Gln Thr Gly Glu
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Leu Leu Leu Lys Thr Ser Val Trp Leu Val Leu Leu Phe Ser Val Met
35 40 45

Gly Leu Trp Gln Val Ser Asn Ala Ala Glu Gln His Thr Pro Met Lys
50 55 60

Ala His Ala Val Thr Thr Ile Asp Lys Ala Thr Thr Asp Lys Gln Gln
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Val Pro Pro Thr Lys Glu Ala Ala His His Ser Gly Lys Glu Ala Ala
85 90 95

Thr Asn Val Ser Ala Ser Ala Gln Gly Thr Ala Asp Asp Thr Asn Ser
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Lys Val Thr Ser Asn Ala Pro Ser Asn Lys Pro Ser Thr Val Val Ser
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Thr Lys Val Asn Glu Thr Arg Asp Val Asp Thr Gln Gln Ala Ser Thr
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Gln Lys Pro Thr His Thr Ala Thr Phe Lys Leu Ser Asn Ala Lys Thr
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Ala Ser Leu Ser Pro Arg Met Phe Ala Ala Asn Ala Pro Gln Thr Thr
165 170 175

Thr His Lys Ile Leu His Thr Asn Asp Ile His Gly Arg Leu Ala Glu
180 185 190

Glu Lys Gly Arg Val Ile Gly Met Ala Lys Leu Lys Thr Val Lys Glu
195 200 205

Gln Glu Lys Pro Asp Leu Met Leu Asp Ala Gly Asp Ala Phe Gln Gly
210 215 220

Leu Pro Leu Ser Asn Gln Ser Lys Gly Glu Glu Met Ala Lys Ala Met

225 230 235 240

Asn Ala Val Gly Tyr Asp Ala Met Ala Val Gly Asn His Glu Phe Asp
245 250 255

Phe Gly Tyr Asp Gln Leu Lys Lys Leu Glu Gly Met Leu Asp Phe Pro
260 265 270

Met Leu Ser Thr Asn Val Tyr Lys Asp Gly Lys Arg Ala Phe Lys Pro
275 280 285

Ser Thr Ile Val Thr Lys Asn Gly Ile Arg Tyr Gly Ile Ile Gly Val
290 295 300

Thr Thr Pro Glu Thr Lys Thr Lys Thr Arg Pro Glu Gly Ile Lys Gly
305 310 315 320

Val Glu Phe Arg Asp Pro Leu Gln Ser Val Thr Ala Glu Met Met Arg
325 330 335

Ile Tyr Lys Asp Val Asp Thr Phe Val Val Ile Ser His Leu Gly Ile
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Asp Pro Ser Thr Gln Glu Thr Trp Arg Gly Asp Tyr Leu Val Lys Gln
355 360 365

Leu Ser Gln Asn Pro Gln Leu Lys Lys Arg Ile Thr Val Ile Asp Gly
370 375 380

His Ser His Thr Val Leu Gln Asn Gly Gln Ile Tyr Asn Asn Asp Ala
385 390 395 400

Leu Ala Gln Thr Gly Thr Ala Leu Ala Asn Ile Gly Lys Ile Thr Phe
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Asn Tyr Arg Asn Gly Glu Val Ser Asn Ile Lys Pro Ser Leu Ile Asn
420 425 430

Val Lys Asp Val Glu Asn Val Thr Pro Asn Lys Ala Leu Ala Glu Gln
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Ile Pro Asn Asn Thr Ile Asp Phe Lys Gly Glu Arg Asp Asp Val Arg
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Thr Arg Glu Thr Asn Leu Gly Asn Ala Ile Ala Asp Ala Met Glu Ala
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Tyr Gly Val Lys Asn Phe Ser Lys Lys Thr Asp Phe Ala Val Thr Asn
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Pro Ser Gly Lys Arg Ile Asn Ala Ile Gln Ile Leu Asn Lys Glu Thr
595 600 605

Gly Lys Phe Glu Asn Ile Asp Leu Lys Arg Val Tyr His Val Thr Met
610 615 620

Asn Asp Phe Thr Ala Ser Gly Gly Asp Gly Tyr Ser Met Phe Gly Gly
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Pro Arg Glu Glu Gly Ile Ser Leu Asp Gln Val Leu Ala Ser Tyr Leu
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Lys Thr Ala Asn Leu Ala Lys Tyr Asp Thr Thr Glu Pro Gln Arg Met
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690 695 700

Asp Lys Val Met Asp Pro Ala Lys Lys Pro Ala Pro Gly Lys Val Val
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725 730 735

Gly Arg Thr Ile Glu Gly Ala Thr Val Ser Ser Lys Ser Gly Lys Gln
740 745 750

Leu Ala Arg Met Ser Val Pro Lys Gly Ser Ala His Glu Lys Gln Leu
755 760 765

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Ser Ile Arg Lys Phe Thr Val Gly Thr Ala Ser Ile Leu Ile Gly Ser
35 40 45

Leu Met Tyr Leu Gly Thr Gln Gln Glu Ala Glu Ala Ala Glu Asn Asn
50 55 60

Ile Glu Asn Pro Thr Thr Leu Lys Asp Asn Val Gln Ser Lys Glu Val
65 70 75 80

```
Lys Ile Glu Glu Val Thr Asn Lys Asp Thr Ala Pro Gln Gly Val Glu
                85                  90                  95

Ala Lys Ser Glu Val Thr Ser Asn Lys Asp Thr Ile Glu His Glu Pro
           100                 105                 110

Ser Val Lys Ala Glu Asp Ile Ser Lys Lys Glu Asp Thr Pro Lys Glu
       115                 120                 125

Val Ala Asp Val Ala Glu Val Gln Pro Lys Ser Ser Val Thr His Asn
   130                 135                 140

Ala Glu Thr Pro Lys Val Arg Lys Ala Arg Ser Val Asp Glu Gly Ser
145                 150                 155                 160

Phe Asp Ile Thr Arg Asp Ser Lys Asn Val Val Glu Ser Thr Pro Ile
                165                 170                 175

Thr Ile Gln Gly Lys Glu His Phe Glu Gly Tyr Gly Ser Val Asp Ile
           180                 185                 190

Gln Lys Lys Pro Thr Asp Leu Gly Val Ser Glu Val Thr Arg Phe Asn
       195                 200                 205

Val Gly Asn Glu Ser Asn Gly Leu Ile Gly Ala Leu Gln Leu Lys Asn
   210                 215                 220

Lys Ile Asp Phe Ser Lys Asp Phe Asn Phe Lys Val Arg Val Ala Asn
225                 230                 235                 240

Asn His Gln Ser Asn Thr Thr Gly Ala Asp Gly Trp Gly Phe Leu Phe
                245                 250                 255

Ser Lys Gly Asn Ala Glu Glu Tyr Leu Thr Asn Gly Gly Ile Leu Gly
           260                 265                 270

Asp Lys Gly Leu Val Asn Ser Gly Gly Phe Lys Ile Asp Thr Gly Tyr
       275                 280                 285

Ile Tyr Thr Ser Ser Met Asp Lys Thr Glu Lys Gln Ala Gly Gln Gly
   290                 295                 300

Tyr Arg Gly Tyr Gly Ala Phe Val Lys Asn Asp Ser Ser Gly Asn Ser
305                 310                 315                 320

Gln Met Val Gly Glu Asn Ile Asp Lys Ser Lys Thr Asn Phe Leu Asn
                325                 330                 335

Tyr Ala Asp Asn Ser Thr Asn Thr Ser Asp Gly Lys Phe His Gly Gln
           340                 345                 350

Arg Leu Asn Asp Val Ile Leu Thr Tyr Val Ala Ser Thr Gly Lys Met
       355                 360                 365

Arg Ala Glu Tyr Ala Gly Lys Thr Trp Glu Thr Ser Ile Thr Asp Leu
   370                 375                 380

Gly Leu Ser Lys Asn Gln Ala Tyr Asn Phe Leu Ile Thr Ser Ser Gln
385                 390                 395                 400
```

Arg Trp Gly Leu Asn Gln Gly Ile Asn Ala Asn Gly Trp Met Arg Thr
405 410 415

Asp Leu Lys Gly Ser Glu Phe Thr Phe Thr Pro Glu Ala Pro Lys Thr
420 425 430

Ile Thr Glu Leu Glu Lys Lys Val Glu Glu Ile Pro Phe Lys Lys Glu
435 440 445

Arg Lys Phe Asn Pro Asp Leu Ala Pro Gly Thr Glu Lys Val Thr Arg
450 455 460

Glu Gly Gln Lys Gly Glu Lys Thr Ile Thr Thr Pro Thr Leu Lys Asn
465 470 475 480

Pro Leu Thr Gly Val Ile Ile Ser Lys Gly Glu Pro Lys Glu Glu Ile
485 490 495

Thr Lys Asp Pro Ile Asn Glu Leu Thr Glu Tyr Gly Pro Glu Thr Ile
500 505 510

Ala Pro Gly His Arg Asp Glu Phe Asp Pro Lys Leu Pro Thr Gly Glu
515 520 525

Lys Glu Glu Val Pro Gly Lys Pro Gly Ile Lys Asn Pro Glu Thr Gly
530 535 540

Asp Val Val Arg Pro Pro Val Asp Ser Val Thr Lys Tyr Gly Pro Val
545 550 555 560

Lys Gly Asp Ser Ile Val Glu Lys Glu Glu Ile Pro Phe Glu Lys Glu
565 570 575

Arg Lys Phe Asn Pro Asp Leu Ala Pro Gly Thr Glu Lys Val Thr Arg
580 585 590

Glu Gly Gln Lys Gly Glu Lys Thr Ile Thr Thr Pro Thr Leu Lys Asn
595 600 605

Pro Leu Thr Gly Glu Ile Ile Ser Lys Gly Glu Ser Lys Glu Glu Ile
610 615 620

Thr Lys Asp Pro Ile Asn Glu Leu Thr Glu Tyr Gly Pro Glu Thr Ile
625 630 635 640

Thr Pro Gly His Arg Asp Glu Phe Asp Pro Lys Leu Pro Thr Gly Glu
645 650 655

Lys Glu Glu Val Pro Gly Lys Pro Gly Ile Lys Asn Pro Glu Thr Gly
660 665 670

Asp Val Val Arg Pro Pro Val Asp Ser Val Thr Lys Tyr Gly Pro Val
675 680 685

Lys Gly Asp Ser Ile Val Glu Lys Glu Glu Ile Pro Phe Glu Lys Glu
690 695 700

Arg Lys Phe Asn Pro Asp Leu Ala Pro Gly Thr Glu Lys Val Thr Arg
705 710 715 720

```
Glu Gly Gln Lys Gly Glu Lys Thr Ile Thr Thr Pro Thr Leu Lys Asn
                725                 730                 735

Pro Leu Thr Gly Val Ile Ile Ser Lys Gly Glu Pro Lys Glu Glu Ile
            740                 745                 750

Thr Lys Asp Pro Ile Asn Glu Leu Thr Glu Tyr Gly Pro Glu Thr Ile
        755                 760                 765

Thr Pro Gly His Arg Asp Glu Phe Asp Pro Lys Leu Pro Thr Gly Glu
    770                 775                 780

Lys Glu Glu Val Pro Gly Lys Pro Gly Ile Lys Asn Pro Glu Thr Gly
785                 790                 795                 800

Asp Val Val Arg Pro Pro Val Asp Ser Val Thr Lys Tyr Gly Pro Val
                805                 810                 815

Lys Gly Asp Ser Ile Val Glu Lys Glu Glu Ile Pro Phe Lys Lys Glu
            820                 825                 830

Arg Lys Phe Asn Pro Asp Leu Ala Pro Gly Thr Glu Lys Val Thr Arg
        835                 840                 845

Glu Gly Gln Lys Gly Glu Lys Thr Ile Thr Thr Pro Thr Leu Lys Asn
    850                 855                 860

Pro Leu Thr Gly Glu Ile Ile Ser Lys Gly Glu Ser Lys Glu Glu Ile
865                 870                 875                 880

Thr Lys Asp Pro Ile Asn Glu Leu Thr Glu Tyr Gly Pro Glu Thr Ile
                885                 890                 895

Thr Pro Gly His Arg Asp Glu Phe Asp Pro Lys Leu Pro Thr Gly Glu
            900                 905                 910

Lys Glu Glu Val Pro Gly Lys Pro Gly Ile Lys Asn Pro Glu Thr Gly
        915                 920                 925

Asp Val Val Arg Pro Pro Val Asp Ser Val Thr Lys Tyr Gly Pro Val
    930                 935                 940

Lys Gly Asp Ser Ile Val Glu Lys Glu Glu Ile Pro Phe Glu Lys Glu
945                 950                 955                 960

Arg Lys Phe Asn Pro Asp Leu Ala Pro Gly Thr Glu Lys Val Thr Arg
                965                 970                 975

Glu Gly Gln Lys Gly Glu Lys Thr Ile Thr Thr Pro Thr Leu Lys Asn
            980                 985                 990

Pro Leu Thr Gly Glu Ile Ile Ser  Lys Gly Glu Ser Lys  Glu Glu Ile
        995                 1000                1005

Thr Lys  Asp Pro Ile Asn Glu  Leu Thr Glu Tyr Gly  Pro Glu Thr
    1010                1015                1020

Ile Thr  Pro Gly His Arg Asp  Glu Phe Asp Pro Lys  Leu Pro Thr
    1025                1030                1035
```

Gly Glu Lys Glu Glu Val Pro Gly Lys Pro Gly Ile Lys Asn Pro
1040 1045 1050

Glu Thr Gly Asp Val Val Arg Pro Pro Val Asp Ser Val Thr Lys
1055 1060 1065

Tyr Gly Pro Val Lys Gly Asp Ser Ile Val Glu Lys Glu Glu Ile
1070 1075 1080

Pro Phe Lys Lys Glu Arg Lys Phe Asn Pro Asp Leu Ala Pro Gly
1085 1090 1095

Thr Glu Lys Val Thr Arg Glu Gly Gln Lys Gly Glu Lys Thr Ile
1100 1105 1110

Thr Thr Pro Thr Leu Lys Asn Pro Leu Thr Gly Glu Ile Ile Ser
1115 1120 1125

Lys Gly Glu Ser Lys Glu Glu Ile Thr Lys Asp Pro Ile Asn Glu
1130 1135 1140

Leu Thr Glu Tyr Gly Pro Glu Thr Ile Thr Pro Gly His Arg Asp
1145 1150 1155

Glu Phe Asp Pro Lys Leu Pro Thr Gly Glu Lys Glu Glu Val Pro
1160 1165 1170

Gly Lys Pro Gly Ile Lys Asn Pro Glu Thr Gly Asp Val Val Arg
1175 1180 1185

Pro Pro Val Asp Ser Val Thr Lys Tyr Gly Pro Val Lys Gly Asp
1190 1195 1200

Ser Ile Val Glu Lys Glu Glu Ile Pro Phe Glu Lys Glu Arg Lys
1205 1210 1215

Phe Asn Pro Asp Leu Ala Pro Gly Thr Glu Lys Val Thr Arg Glu
1220 1225 1230

Gly Gln Lys Gly Glu Lys Thr Ile Thr Thr Pro Thr Leu Lys Asn
1235 1240 1245

Pro Leu Thr Gly Glu Ile Ile Ser Lys Gly Glu Ser Lys Glu Glu
1250 1255 1260

Ile Thr Lys Asp Pro Ile Asn Glu Leu Thr Glu Tyr Gly Pro Glu
1265 1270 1275

Thr Ile Thr Pro Gly His Arg Asp Glu Phe Asp Pro Lys Leu Pro
1280 1285 1290

Thr Gly Glu Lys Glu Glu Val Pro Gly Lys Pro Gly Ile Lys Asn
1295 1300 1305

Pro Glu Thr Gly Asp Val Val Arg Pro Pro Val Asp Ser Val Thr
1310 1315 1320

Lys Tyr Gly Pro Val Lys Gly Asp Ser Ile Val Glu Lys Glu Glu
1325 1330 1335

```
Ile Pro  Phe Glu Lys Glu Arg  Lys Phe Asn Pro Asp  Leu Ala Pro
1340                 1345                 1350

Gly Thr  Glu Lys Val Thr Arg  Glu Gly Gln Lys Gly  Glu Lys Thr
1355                 1360                 1365

Ile Thr  Thr Pro Thr Leu Lys  Asn Pro Leu Thr Gly  Glu Ile Ile
1370                 1375                 1380

Ser Lys  Gly Glu Ser Lys Glu  Glu Ile Thr Lys Asp  Pro Val Asn
1385                 1390                 1395

Glu Leu  Thr Glu Phe Gly Gly  Glu Lys Ile Pro Gln  Gly His Lys
1400                 1405                 1410

Asp Ile  Phe Asp Pro Asn Leu  Pro Thr Asp Gln Thr  Glu Lys Val
1415                 1420                 1425

Pro Gly  Lys Pro Gly Ile Lys  Asn Pro Asp Thr Gly  Lys Val Ile
1430                 1435                 1440

Glu Glu  Pro Val Asp Asp Val  Ile Lys His Gly Pro  Lys Thr Gly
1445                 1450                 1455

Thr Pro  Glu Thr Lys Thr Val  Glu Ile Pro Phe Glu  Thr Lys Arg
1460                 1465                 1470

Glu Phe  Asn Pro Lys Leu Gln  Pro Gly Glu Glu Arg  Val Lys Gln
1475                 1480                 1485

Glu Gly  Gln Pro Gly Ser Lys  Thr Ile Thr Thr Pro  Ile Thr Val
1490                 1495                 1500

Asn Pro  Leu Thr Gly Glu Lys  Val Gly Glu Gly Gln  Pro Thr Glu
1505                 1510                 1515

Glu Ile  Thr Lys Gln Pro Val  Asp Lys Ile Val Glu  Phe Gly Gly
1520                 1525                 1530

Glu Lys  Pro Lys Asp Pro Lys  Gly Pro Glu Asn Pro  Glu Lys Pro
1535                 1540                 1545

Ser Arg  Pro Thr His Pro Ser  Gly Pro Val Asn Pro  Asn Asn Pro
1550                 1555                 1560

Gly Leu  Ser Lys Asp Arg Ala  Lys Pro Asn Gly Pro  Val His Ser
1565                 1570                 1575

Met Asp  Lys Asn Asp Lys Val  Lys Lys Ser Lys Ile  Ala Lys Glu
1580                 1585                 1590

Ser Val  Ala Asn Gln Glu Lys  Lys Arg Ala Glu Leu  Pro Lys Thr
1595                 1600                 1605

Gly Leu  Glu Ser Thr Gln Lys  Gly Leu Ile Phe Ser  Ser Ile Ile
1610                 1615                 1620

Gly Ile  Ala Gly Leu Met Leu  Leu Ala Arg Arg Arg  Lys Asn
1625                 1630                 1635
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<210> 15
<211> 1923
<212> DNA
<213> Staphylococcus epidermidis

<400> 15
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tcgtgttcga caatgatggc gacaagtatc attttaacga atatcttgcc gtacgatgcc 120
caagctgcat ctgaaaagga tactgaaatt acaaaagaga tattatctaa gcaagattta 180
ttagacaaag ttgacaaggc aattcgtcaa attgagcaat taaaacagtt atcggcttca 240
tctaaagaac attataaagc acaactaaat gaagcgaaaa cagcatcgca aatagatgaa 300
atcataaaac gagctaatga gttggatagc aaagacaata aaagttctca cactgaaatg 360
aacggtcaaa gtgatataga cagtaaatta gatcaattgc ttaaagattt aaatgaggtt 420
tcttcaaatg ttgatagggg tcaacaaagt ggcgaggacg atcttaatgc aatgaaaaat 480
gatatgtcac aaacggctac aacaaaacat ggagaaaaag atgataaaaa tgatgaagca 540
atggtaaata aggcgttaga agacctagac catttgaatc agcaaataca caaatcgaaa 600
gatgcatcga aagatacatc ggaagatcca gcagtgtcta caacagataa taatcatgaa 660
gtagctaaaa cgccaaataa tgatggttct ggacatgttg tgttaaataa attcctttca 720
aatgaagaga atcaaagcca tagtaatcga ctcactgata aattacaagg aagcgataaa 780
attaatcatg ctatgattga aaaattagct aaaagtaatg cctcaacgca acattacaca 840
tatcataaac tgaatacgtt acaatcttta gatcaacgta ttgcaaatac gcaacttcct 900
aaaaatcaaa aatcagactt aatgagcgaa gtaaataaga cgaaagagcg tataaaaagt 960
caacgaaata ttattttgga agaacttgca cgtactgatg ataaaaagta tgctacacaa 1020
agcattttag aaagtatatt taataaagac gaggcagtta aaattctaaa agatatacgt 1080
gttgatggta aaacagatca acaaattgca gatcaaatta ctcgtcatat tgatcaatta 1140
tctctgacaa cgagtgatga tttattaacg tcattgattg atcaatcaca agataagtcg 1200
ctattgattt ctcaaatttt acaaacgaaa ttaggaaaag ctgaagcaga taaattggct 1260
aaagattgga cgaataaagg attatcaaat cgccaaatcg ttgaccaatt gaagaaacat 1320
tttgcatcaa ctggcgacac gtcttcagat gatatattaa aagcaatttt gaataatgcc 1380
aaagataaaa aacaagcaat tgaaacgatt ttagcaacac gtatagaaag acaaaaggca 1440
aaattactgg cagatttaat tactaaaata gaaacagatc aaaataaaat ttttaattta 1500
gttaaatcgg cattgaatgg taaagcggat gatttattga atttacaaaa gagactcaat 1560
caaacgaaaa aagatataga ttatatttta tcaccaatag taaatcgtcc aagtttacta 1620

gatcgattga ataaaaatgg gaaaacgaca gatttaaata agttagcaaa tttaatgaat 1680

caaggatcag atttattaga cagtattcca gatataccca caccaaagcc agaaaagacg 1740

ttaacacttg gtaaaggtaa tggattgtta agtggattat taaatgctga tggtaatgta 1800

tctttgccta aagcggggga aacgataaaa gaacattggt tgccgatatc tgtaattgtt 1860

ggtgcaatgg gtgtactaat gatttggtta tcacgacgca ataagttgaa aaataaagca 1920

taa 1923

<210> 16
<211> 640
<212> PRT
<213> Staphylococcus epidermidis

<400> 16

Gly Arg Ser Met Leu Met Ala Lys Tyr Arg Gly Lys Pro Phe Gln Leu
1 5 10 15

Tyr Val Lys Leu Ser Cys Ser Thr Met Met Ala Thr Ser Ile Ile Leu
20 25 30

Thr Asn Ile Leu Pro Tyr Asp Ala Gln Ala Ala Ser Glu Lys Asp Thr
35 40 45

Glu Ile Thr Lys Glu Ile Leu Ser Lys Gln Asp Leu Leu Asp Lys Val
50 55 60

Asp Lys Ala Ile Arg Gln Ile Glu Gln Leu Lys Gln Leu Ser Ala Ser
65 70 75 80

Ser Lys Glu His Tyr Lys Ala Gln Leu Asn Glu Ala Lys Thr Ala Ser
85 90 95

Gln Ile Asp Glu Ile Ile Lys Arg Ala Asn Glu Leu Asp Ser Lys Asp
100 105 110

Asn Lys Ser Ser His Thr Glu Met Asn Gly Gln Ser Asp Ile Asp Ser
115 120 125

Lys Leu Asp Gln Leu Leu Lys Asp Leu Asn Glu Val Ser Ser Asn Val
130 135 140

Asp Arg Gly Gln Gln Ser Gly Glu Asp Asp Leu Asn Ala Met Lys Asn
145 150 155 160

Asp Met Ser Gln Thr Ala Thr Thr Lys His Gly Glu Lys Asp Asp Lys
165 170 175

Asn Asp Glu Ala Met Val Asn Lys Ala Leu Glu Asp Leu Asp His Leu
180 185 190

Asn Gln Gln Ile His Lys Ser Lys Asp Ala Ser Lys Asp Thr Ser Glu
195 200 205

Asp Pro Ala Val Ser Thr Thr Asp Asn Asn His Glu Val Ala Lys Thr

```
     210                 215                 220

Pro Asn Asn Asp Gly Ser Gly His Val Val Leu Asn Lys Phe Leu Ser
225                 230                 235                 240

Asn Glu Glu Asn Gln Ser His Ser Asn Arg Leu Thr Asp Lys Leu Gln
                245                 250                 255

Gly Ser Asp Lys Ile Asn His Ala Met Ile Glu Lys Leu Ala Lys Ser
            260                 265                 270

Asn Ala Ser Thr Gln His Tyr Thr Tyr His Lys Leu Asn Thr Leu Gln
        275                 280                 285

Ser Leu Asp Gln Arg Ile Ala Asn Thr Gln Leu Pro Lys Asn Gln Lys
    290                 295                 300

Ser Asp Leu Met Ser Glu Val Asn Lys Thr Lys Glu Arg Ile Lys Ser
305                 310                 315                 320

Gln Arg Asn Ile Ile Leu Glu Glu Leu Ala Arg Thr Asp Asp Lys Lys
                325                 330                 335

Tyr Ala Thr Gln Ser Ile Leu Glu Ser Ile Phe Asn Lys Asp Glu Ala
            340                 345                 350

Val Lys Ile Leu Lys Asp Ile Arg Val Asp Gly Lys Thr Asp Gln Gln
        355                 360                 365

Ile Ala Asp Gln Ile Thr Arg His Ile Asp Gln Leu Ser Leu Thr Thr
    370                 375                 380

Ser Asp Asp Leu Leu Thr Ser Leu Ile Asp Gln Ser Gln Asp Lys Ser
385                 390                 395                 400

Leu Leu Ile Ser Gln Ile Leu Gln Thr Lys Leu Gly Lys Ala Glu Ala
                405                 410                 415

Asp Lys Leu Ala Lys Asp Trp Thr Asn Lys Gly Leu Ser Asn Arg Gln
            420                 425                 430

Ile Val Asp Gln Leu Lys Lys His Phe Ala Ser Thr Gly Asp Thr Ser
        435                 440                 445

Ser Asp Asp Ile Leu Lys Ala Ile Leu Asn Asn Ala Lys Asp Lys Lys
    450                 455                 460

Gln Ala Ile Glu Thr Ile Leu Ala Thr Arg Ile Glu Arg Gln Lys Ala
465                 470                 475                 480

Lys Leu Leu Ala Asp Leu Ile Thr Lys Ile Glu Thr Asp Gln Asn Lys
                485                 490                 495

Ile Phe Asn Leu Val Lys Ser Ala Leu Asn Gly Lys Ala Asp Asp Leu
            500                 505                 510

Leu Asn Leu Gln Lys Arg Leu Asn Gln Thr Lys Lys Asp Ile Asp Tyr
        515                 520                 525

Ile Leu Ser Pro Ile Val Asn Arg Pro Ser Leu Leu Asp Arg Leu Asn
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530 535 540

Lys Asn Gly Lys Thr Thr Asp Leu Asn Lys Leu Ala Asn Leu Met Asn
545 550 555 560

Gln Gly Ser Asp Leu Leu Asp Ser Ile Pro Asp Ile Pro Thr Pro Lys
565 570 575

Pro Glu Lys Thr Leu Thr Leu Gly Lys Gly Asn Gly Leu Leu Ser Gly
580 585 590

Leu Leu Asn Ala Asp Gly Asn Val Ser Leu Pro Lys Ala Gly Glu Thr
595 600 605

Ile Lys Glu His Trp Leu Pro Ile Ser Val Ile Val Gly Ala Met Gly
610 615 620

Val Leu Met Ile Trp Leu Ser Arg Arg Asn Lys Leu Lys Asn Lys Ala
625 630 635 640

<210> 17
<211> 522
<212> PRT
<213> Staphylococcus epidermidis

<400> 17

Ala Ser Glu Thr Pro Ile Thr Ser Glu Ile Ser Ser Asn Ser Glu Thr
1 5 10 15

Val Ala Asn Gln Asn Ser Thr Thr Ile Lys Asn Ser Gln Lys Glu Thr
20 25 30

Val Asn Ser Thr Ser Leu Glu Ser Asn His Ser Asn Ser Thr Asn Lys
35 40 45

Gln Met Ser Ser Glu Val Thr Asn Thr Ala Gln Ser Ser Glu Lys Ala
50 55 60

Gly Ile Ser Gln Gln Ser Ser Glu Thr Ser Asn Gln Ser Ser Lys Leu
65 70 75 80

Asn Thr Tyr Ala Ser Thr Asp His Val Glu Ser Thr Thr Ile Asn Asn
85 90 95

Asp Asn Thr Ala Gln Gln Asp Gln Asn Lys Ser Ser Asn Val Thr Ser
100 105 110

Lys Ser Thr Gln Ser Asn Thr Ser Ser Ser Glu Lys Asn Ile Ser Ser
115 120 125

Asn Leu Thr Gln Ser Ile Glu Thr Lys Ala Thr Asp Ser Leu Ala Thr
130 135 140

Ser Glu Ala Arg Thr Ser Thr Asn Gln Ile Ser Asn Leu Thr Ser Thr
145 150 155 160

Ser Thr Ser Asn Gln Ser Ser Pro Thr Ser Phe Ala Asn Leu Arg Thr
165 170 175

```
Phe Ser Arg Phe Thr Val Leu Asn Thr Met Ala Ala Pro Thr Thr Thr
            180                 185                 190

Ser Thr Thr Thr Thr Ser Ser Leu Thr Ser Asn Ser Val Val Val Asn
        195                 200                 205

Lys Asp Asn Phe Asn Glu His Met Asn Leu Ser Gly Ser Ala Thr Tyr
    210                 215                 220

Asp Pro Lys Thr Gly Ile Ala Thr Leu Thr Pro Asp Ala Tyr Ser Gln
225                 230                 235                 240

Lys Gly Ala Ile Ser Leu Asn Thr Arg Leu Asp Ser Asn Arg Ser Phe
                245                 250                 255

Arg Phe Ile Gly Lys Val Asn Leu Gly Asn Arg Tyr Glu Gly Tyr Ser
            260                 265                 270

Pro Asp Gly Val Ala Gly Gly Asp Gly Ile Gly Phe Ala Phe Ser Pro
        275                 280                 285

Gly Pro Leu Gly Gln Ile Gly Lys Glu Gly Ala Ala Val Gly Ile Gly
    290                 295                 300

Gly Leu Asn Asn Ala Phe Gly Phe Lys Leu Asp Thr Tyr His Asn Thr
305                 310                 315                 320

Ser Thr Pro Arg Ser Asp Ala Lys Ala Lys Ala Asp Pro Arg Asn Val
                325                 330                 335

Gly Gly Gly Gly Ala Phe Gly Ala Phe Val Ser Thr Asp Arg Asn Gly
            340                 345                 350

Met Ala Thr Thr Glu Glu Ser Thr Ala Ala Lys Leu Asn Val Gln Pro
        355                 360                 365

Thr Asp Asn Ser Phe Gln Asp Phe Val Ile Asp Tyr Asn Gly Asp Thr
    370                 375                 380

Lys Val Met Thr Val Thr Tyr Ala Gly Gln Thr Phe Thr Arg Asn Leu
385                 390                 395                 400

Thr Asp Trp Ile Lys Asn Ser Gly Gly Thr Thr Phe Ser Leu Ser Met
                405                 410                 415

Thr Ala Ser Thr Gly Gly Ala Lys Asn Leu Gln Gln Val Gln Phe Gly
            420                 425                 430

Thr Phe Glu Tyr Thr Glu Ser Ala Val Ala Lys Val Arg Tyr Val Asp
        435                 440                 445

Ala Asn Thr Gly Lys Asp Ile Ile Pro Pro Lys Thr Ile Ala Gly Glu
    450                 455                 460

Val Asp Gly Thr Val Asn Ile Asp Lys Gln Leu Asn Asn Phe Lys Asn
465                 470                 475                 480

Leu Gly Tyr Ser Tyr Val Gly Thr Asp Ala Leu Lys Ala Pro Asn Tyr
                485                 490                 495
```

Thr Glu Thr Ser Gly Thr Pro Thr Leu Lys Leu Thr Asn Ser Ser Gln
500 505 510

Thr Val Ile Tyr Lys Phe Lys Asp Val Gln
515 520

<210> 18
<211> 485
<212> PRT
<213> Staphylococcus epidermidis

<400> 18

Ala Ser Asp Ala Pro Leu Thr Ser Glu Leu Asn Thr Gln Ser Glu Thr
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Val Gly Asn Gln Asn Ser Thr Thr Ile Glu Ala Ser Thr Ser Thr Ala
20 25 30

Asp Ser Thr Ser Val Thr Lys Asn Ser Ser Ser Val Gln Thr Ser Asn
35 40 45

Ser Asp Thr Val Ser Ser Glu Lys Ser Glu Lys Val Thr Ser Thr Thr
50 55 60

Asn Ser Thr Ser Asn Gln Gln Glu Lys Leu Thr Ser Thr Ser Glu Ser
65 70 75 80

Thr Ser Ser Lys Asn Thr Thr Ser Ser Ser Asp Thr Lys Ser Val Ala
85 90 95

Ser Thr Ser Ser Thr Glu Gln Pro Ile Asn Thr Ser Thr Asn Gln Ser
100 105 110

Thr Ala Ser Asn Asn Thr Ser Gln Ser Thr Thr Pro Ser Ser Val Asn
115 120 125

Leu Asn Lys Thr Ser Thr Thr Ser Thr Ser Thr Ala Pro Val Lys Leu
130 135 140

Arg Thr Phe Ser Arg Leu Ala Met Ser Thr Phe Ala Ser Ala Ala Thr
145 150 155 160

Thr Thr Ala Val Thr Ala Asn Thr Ile Thr Val Asn Lys Asp Asn Leu
165 170 175

Lys Gln Tyr Met Thr Thr Ser Gly Asn Ala Thr Tyr Asp Gln Ser Thr
180 185 190

Gly Ile Val Thr Leu Thr Gln Asp Ala Tyr Ser Gln Lys Gly Ala Ile
195 200 205

Thr Leu Gly Thr Arg Ile Asp Ser Asn Lys Ser Phe His Phe Ser Gly
210 215 220

Lys Val Asn Leu Gly Asn Lys Tyr Glu Gly His Gly Asn Gly Gly Asp
225 230 235 240

Gly Ile Gly Phe Ala Phe Ser Pro Gly Val Leu Gly Glu Thr Gly Leu
245 250 255

```
Asn Gly Ala Ala Val Gly Ile Gly Gly Leu Ser Asn Ala Phe Gly Phe
            260                 265                 270

Lys Leu Asp Thr Tyr His Asn Thr Ser Lys Pro Asn Ser Ala Ala Lys
        275                 280                 285

Ala Asn Ala Asp Pro Ser Asn Val Ala Gly Gly Gly Ala Phe Gly Ala
    290                 295                 300

Phe Val Thr Thr Asp Ser Tyr Gly Val Ala Thr Thr Tyr Thr Ser Ser
305                 310                 315                 320

Ser Thr Ala Asp Asn Ala Ala Lys Leu Asn Val Gln Pro Thr Asn Asn
                325                 330                 335

Thr Phe Gln Asp Phe Asp Ile Asn Tyr Asn Gly Asp Thr Lys Val Met
            340                 345                 350

Thr Val Lys Tyr Ala Gly Gln Thr Trp Thr Arg Asn Ile Ser Asp Trp
        355                 360                 365

Ile Ala Lys Ser Gly Thr Thr Asn Phe Ser Leu Ser Met Thr Ala Ser
    370                 375                 380

Thr Gly Gly Ala Thr Asn Leu Gln Gln Val Gln Phe Gly Thr Phe Glu
385                 390                 395                 400

Tyr Thr Glu Ser Ala Val Thr Gln Val Arg Tyr Val Asp Val Thr Thr
                405                 410                 415

Gly Lys Asp Ile Ile Pro Pro Lys Thr Tyr Ser Gly Asn Val Asp Gln
            420                 425                 430

Val Val Thr Ile Asp Asn Gln Gln Ser Ala Leu Thr Ala Lys Gly Tyr
        435                 440                 445

Asn Tyr Thr Ser Val Asp Ser Ser Tyr Ala Ser Thr Tyr Asn Asp Thr
    450                 455                 460

Asn Lys Thr Val Lys Met Thr Asn Ala Gly Gln Ser Val Thr Tyr Tyr
465                 470                 475                 480

Phe Thr Asp Val Val
                485

<210>  19
<211>  1245
<212>  PRT
<213>  Staphylococcus epidermidis

<400>  19

Met Gly Lys Arg Arg Gln Gly Pro Ile Asn Lys Lys Val Asp Phe Leu
1               5                   10                  15

Pro Asn Lys Leu Asn Lys Tyr Ser Ile Arg Lys Phe Thr Val Gly Thr
            20                  25                  30

Ala Ser Ile Leu Leu Gly Ser Thr Leu Ile Phe Gly Ser Ser Ser His
```

```
          35                  40                  45

Glu Ala Lys Ala Ala Glu Glu Lys Gln Val Asp Pro Ile Thr Gln Ala
    50                  55                  60

Asn Gln Asn Asp Ser Ser Glu Arg Ser Leu Glu Asn Thr Asn Gln Pro
65                  70                  75                  80

Thr Val Asn Asn Glu Ala Pro Gln Met Ser Ser Thr Leu Gln Ala Glu
                85                  90                  95

Glu Gly Ser Asn Ala Glu Ala Pro Gln Ser Glu Pro Thr Lys Ala Glu
            100                 105                 110

Glu Gly Gly Asn Ala Glu Ala Ala Gln Ser Glu Pro Thr Lys Ala Glu
        115                 120                 125

Glu Gly Gly Asn Ala Glu Ala Pro Gln Ser Glu Pro Thr Lys Ala Glu
    130                 135                 140

Glu Gly Gly Asn Ala Glu Ala Ala Gln Ser Glu Pro Thr Lys Thr Glu
145                 150                 155                 160

Glu Gly Ser Asn Val Lys Ala Ala Gln Ser Glu Pro Thr Lys Ala Glu
                165                 170                 175

Glu Gly Ser Asn Ala Glu Ala Pro Gln Ser Glu Pro Thr Lys Thr Glu
            180                 185                 190

Glu Gly Ser Asn Ala Lys Ala Ala Gln Ser Glu Pro Thr Lys Ala Glu
        195                 200                 205

Glu Gly Gly Asn Ala Glu Ala Ala Gln Ser Glu Pro Thr Lys Thr Glu
    210                 215                 220

Glu Gly Ser Asn Ala Glu Ala Pro Gln Ser Glu Pro Thr Lys Ala Glu
225                 230                 235                 240

Glu Gly Gly Asn Ala Glu Ala Pro Gln Ser Glu Pro Thr Lys Thr Glu
                245                 250                 255

Glu Gly Gly Asn Ala Glu Ala Pro Asn Val Pro Thr Ile Lys Ala Asn
            260                 265                 270

Ser Asp Asn Asp Thr Gln Thr Gln Phe Ser Glu Ala Pro Thr Arg Asn
        275                 280                 285

Asp Leu Ala Arg Lys Glu Asp Ile Pro Ala Val Ser Lys Asn Glu Glu
    290                 295                 300

Leu Gln Ser Ser Gln Pro Asn Thr Asp Ser Lys Ile Glu Pro Thr Thr
305                 310                 315                 320

Ser Glu Pro Val Asn Leu Asn Tyr Ser Ser Pro Phe Met Ser Leu Leu
                325                 330                 335

Ser Met Pro Ala Asp Ser Ser Ser Asn Asn Thr Lys Asn Thr Ile Asp
            340                 345                 350

Ile Pro Pro Thr Thr Val Lys Gly Arg Asp Asn Tyr Asp Phe Tyr Gly
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```
          355                 360                 365

Arg Val Asp Ile Glu Ser Asn Pro Thr Asp Leu Asn Ala Thr Asn Leu
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2002 (27.12.2002)

PCT

(10) International Publication Number
WO 2002/102829 A3

(51) International Patent Classification[7]: G01N 33/569, C12N 5/06, 5/16, C07K 16/00

(21) International Application Number: PCT/US2002/019220

(22) International Filing Date: 17 June 2002 (17.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/298,098 15 June 2001 (15.06.2001) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 25 March 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CROSS-REACTIVE MONOCLONAL AND POLYCLONAL ANTIBODIES WHICH RECOGNIZE SURFACE PROTEINS FROM COAGULASE-NEGATIVE STAPHYLOCOCCI AND STAPHYLOCOCCUS AUREUS

(57) Abstract: Polyclonal and monoclonal antibodies which are cross-reactive to both coagulase-positive staphylococcus bacteria, such as S. *hemolyticus*, are provided which can recognize surface proteins from both coagulase-positive and coagulase negative staph bacteria. The antibodies may be generated from surface proteins that have been isolated on the basis of characteristics that may be common between S. *aureus* and coagulase-negative staphylococci, and these recombinant surface proteins are used to generate the antibodies of the invention. There is also provided vaccines and methods which utilize these proteins and antibodies for the treatment or protection against a wide variety of staphylococcal infections.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/19220

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : G01 N 33/569; C12 N 5/06, 5/16; C07 K 16/00
US CL : 435/7.33, 326, 332, 530/388.2, 388.4

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/7.33, 326, 332, 530/388.2, 388.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q9L470, 100% identical to SEQ.ID.NO: 21, SEQ.ID.NO: 19.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99QY4, 99.8% identical to SEQ.ID.NO: 18.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99QZ2, 97.4% identical to SEQ.ID.NO: 16.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99XE9, 92 % identical to SEQ.ID.NO: 12.	1-16, 19 and 21

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search
28 September 2003 (28.09.2003)

Date of mailing of the international search report
19 FEB 2004

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PCT/US02/19220

INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99UX5, 97.8 % identical to SEQ.ID.NO: 10.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99UX4, 98.8 % identical to SEQ.ID.NO: 8.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q931P4 96.7 % identical to SEQ.ID.NO: 6 and Accession number Q99TD3, 96.6 % identical to SEQ.ID.NO: 6	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99QY4, 98.6 % identical to SEQ.ID.NO: 4.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99TB0, 91.6 % identical to SEQ.ID.NO: 2.	1-16, 19 and 21
Y	OHLSEN. K. et al Effects of subinhibitory concentrations of antibiotics on alpha-toxin (hla) gene expression of methicillin-sensitive and methicillin-resistant Staphylococcus aureus isolates.Antimicrob Agents Chemother, November1998 , Vol 42, No.11, pages 2817-2823.	1-16, 19 and 21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/19220

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: Please See Continuation Sheet

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions 1-58 which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups 1- 21 Claim(s) 1-14, 16, 19, 21 and 15, drawn to an isolated antibodies that bind to SEQ.ID.NOS: 2, 4, 6,8,10, 12, 14, 16, 17, 18, 19, 21, nucleic acid sequence encoding amino acid sequences SEQ.ID.NOS: 1, 3, 5,7,9, 11, 13, 15, 20 and the nucleic sequences coding for the A domain of the Aap protein or degenerate.

Groups 22-33 Claims 20 and 22 drawn to fragment of the DsqA protein and a vaccine comprising a protein SEQ.ID.NOS: 2, 4, 6,8,10, 12, 14, 16, 17, 18, 19 and 21

Groups 34-45 Claim 17drawn to a method for treating or preventing S.aureus infection using antibodies that bind to SEQ.ID.NOS: 2, 4, 6,8,10, 12, 14, 16, 17, 18, 19 and 21.

Groups 46-57 Claim 18 drawn to a method inducing an immune response using protein SEQ.ID.NOS: 2, 4, 6,8,10, 12, 14, 16, 17, 18, 19 and 21.

The inventions listed as Groups 1-58 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group 1, claim(s) 1-14, 16, 19, 21 and 15, claim(s) 1-14, 16, 19, 21 drawn to an isolated antibodies that bind to SEQ.ID.NOS: 2, diagnostic kit comprising antibody to SEQ.ID.NOS: 2, pharmaceutical compostion comprising said antibody and a method of diagnosing S.aureus infection using said antibody which is the first product and first product of use.

Pursuant to PCT Rule 13.2 the ISA/US considers that where multiple products, processes and methods are claimed, the main invention shall consists of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto. Accordingly the main invention (Group 1) comprises the first product and a method of use.

Further pursuant to PCT Rule 13.2 the ISA/US considers that any feature which the subsequently recited products and methods share with the main invention does not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention. Therefore, the groups of inventions below do not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention.

Groups 2-21 drawn to different isolated antibodies that bind to SEQ.ID.NOS: 4, 6,8,10, 12, 14, 16, 17, 18, 19, 21, nucleic acid sequence encoding amino acid sequences SEQ.ID.NOS: 1, 3, 5,7,9, 11, 13, 15, 20 and the nucleic sequences coding for the A domain of the Aap protein or degenerate that are different to each other and lack the same or corresponding special technical features because each antibody bind to a protein having a specific amino acid sequence. They are structurally different to each other since each sequence has been identified with a specific sequence identification number that contains specific amino acids. In the instant case the different inventions represent structurally different antibodies that bind to different polypeptides. Therefore, where structural identity is required, such as for expression, the different sequences have different effects. Thus, each sequence is unique and lacks the same or corresponding special technical features.

Groups 22-33 drawn to fragment of the DsqA protein and a vaccine comprising a protein SEQ.ID.NOS: 2, 4, 6,8,10, 12, 14, 16, 17, 18, 19, and 21. These proteins are different to each other and lack the same or corresponding special technical features because each protein contains a specific amino acid sequence. They are structurally different to each other since each sequence has been identified with a specific sequence identification number that contains specific amino acids. In the instant case the different inventions represent structurally different proteins. Therefore, where structural identity is required, such as for expression, the different sequences have different effects. Thus, each sequence is unique and lacks the same or corresponding special technical features

INTERNATIONAL SEARCH REPORT

Groups 34-45 and 46-57 are different methods utilizing different products of antibodies or proteins that are unique and lack the same or corresponding special technical features that result in a different outcome such as preventing an infection with antibody or inducing an immune response with specific protein. These methods are different to each other in utilizing different reagents such as different polypeptides and antibodies as discussed above and thus lack the same or special technical features as explained above.

Continuation of Box II Item 3:
1-16, 19 and 21 with respect to SEQ.ID.NOS: 2, 4, 6, 8, 10, 12,16, 18, 19 and 21

Continuation of B. FIELDS SEARCHED Item 3:
SEQ.ID.NOS: 2, 4, 6, 8, 10, 12, 14, 16, 19, 17, 18 and 21 searched on MEDLINE, STN, A -GENSEQ, N-GENSEQ,EST, DERWENT, SWISS-PROT, PIR, USPTOWEST, SWISSSPTREMBL, GENEMBEL, PUBLISHED APPLICATIONS AND ISSUED PATENTS